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(57) Abstract

The present invention is directed to novel human DNA sequences encoding a voltage–gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt–like macular dystrophy, cone–rod macular dystrophy, and Salla disease.

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TITLE OF THE INVENTION

NOVEL HUMAN VOLTAGE-GATED POTASSIUM CHANNEL

CROSS-REFERENCE TO RELATED APPLICATIONS

Not applicable.

STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not applicable.

REFERENCE TO MICROFICHE APPENDIX

Not applicable.

FIELD OF THE INVENTION

The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel.

BACKGROUND OF THE INVENTION

Voltage-gated potassium channels form transmembrane pores that open in response to changes in cell membrane potential and selectively allow potassium ions to pass through the membrane. Many voltage-gated potassium channels have been identified. They are distinguishable by tissue-specific patterns of expression as well as by electrophysiological and pharmacological properties.

Voltage-gated potassium channels have been shown to be involved in maintaining cell membrane potentials and controlling the repolarization of action potentials in many cells, *e.g.*, neurons, muscle cells, and pancreatic β cells. They are important targets for drug discovery in connection with a variety of diseases.

Functional voltage-gated potassium channels are believed to be tetramers of four alpha subunits, each of which contains six transmembrane spanning segments. The alpha subunits making up a tetramer may be the same (in the case of homotetramers) or may be different (in the case of heterotetramers). The membrane-spanning alpha subunits making up the tetramers may sometimes be associated with additional, beta subunits, which may alter the behavior of the tetramers.

For reviews of voltage-gated potassium channels see Robertson, 1997, Trends Pharmacol. Sci. 18:474-483; Jan & Jan, 1997, J. Physiol. 505:267-282; Catterall, 1995, Ann. Rev. Biochem. 64:493-531.

Macular dystrophy is a term applied to a heterogeneous group of diseases that collectively are the cause of severe visual loss in a large number of people. A common characteristic of macular dystrophy is a progressive loss of central vision resulting from the degeneration of the pigmented epithelium underlying the retinal macula. In many forms of macular dystrophy, the end stage of the disease results in legal blindness. More than 20 types of macular dystrophy are known: e.g., age-related macular dystrophy, Stargardt's and Stargardt-like macular dystrophy, cone-rod dystrophies, atypical vitelliform macular dystrophy (VMD1), Usher Syndrome Type 1B, autosomal dominant neovascular inflammatory vitreoretinopathy, familial exudative vitreoretinopathy, and Best's macular dystrophy. For a review of the macular dystrophies, see Sullivan & Daiger, 1996, Mol. Med. Today 2:380-386.

Cone-rod dystrophies involve an initial loss of cone photoreceptors followed by the degeneration of rod photoreceptors. This loss of photoreceptors can lead to blindness. Cone-rod dystrophies appear to be a heterogeneous group of inherited disorders for which multiple chromosomal locations have been implicated (Evans et al., 1994, Nature Genet. 6:210-213; Kelsell et al., 1997, Hum. Mol. Genet. 6:597-600). In particular, Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279 found a candidate gene (CORD7) located at chromosome 6q in a four-generation British family affected with cone-rod dystrophy. A marker in 6q, D6S280, showed a high LOD score of 3.31 (at genetic distance = 0).

Stargardt-like macular dystrophy is an inherited, dominant retinal disease. Affected individuals have normal vision in early childhood but show impaired central vision either in late childhood or early adulthood. The first observable characteristics of the disease are flecks seen in the macula. This is followed by central atrophy, resulting in visual acuity decreasing to 20/200 or worse (Stone et al., Arch. Ophthalmol. 112:765-772 [Stone]). Stone mapped a gene responsible for Stargardt-like macular dystrophy to chromosome 6q. The marker D6S280 was observed by Stone to have the high LOD score of 5.5 (at genetic distance = 0).

Cone-rod dystrophy and Stargardt-like macular dystrophy appear different from a clinical perspective. For example, Stargardt-like macular dystrophy

generally begins in childhood and involves white/yellow flecks in the retina while cone-rod dystrophy is an adult-onset disorder in which no flecks are present. Despite such clinical differences, both diseases may be caused by mutations in the same gene. It is not uncommon for different mutations in a single gene to give rise to clinically different disorders. For example, depending upon the particular mutation, mutations in the peripherin/RDS gene can give rise to either butterfly-shaped pigment dystrophy of the fovea, retinitis pigmentosa, pattern dystrophy, flavus maculatus, macular dystrophy, or central areolar choroidal dystrophy (Nichols et al., 1993, Nature Genet. 3:202-207; Weleber et al., 1993, Arch. Ophtalmol. 111:1531-1542; Wells et al., 1993, Nature Genet. 3:213-218; Reig et al., 1995, Ophthalmic. Genet. 16:39-44).

While studies of macular dystrophies such as cone-rod dystrophy or Stargardt-like macular dystrophy are valuable in themselves, such studies are also valuable in that they are expected to shed light on age-related macular degeneration (AMD). AMD is the leading cause of severe visual loss in older individuals. Genetic factors apparently play a role in AMD (Hyman et al., 1983, Am. J. Epidemiol. 118:213-227; Gass, 1973, Arch. Ophthamol. 90:206-217). It is believed likely that mild allelic variations of such earlier-onset diseases as cone-rod dystrophy and Stargardt-like macular dystrophy are responsible for some cases of AMD. Thus, understanding and developing treatments for these earlier-onset diseases should prove valuable with respect to AMD as well.

Salla disease is a recessive condition characterized by early-onset psychomotor retardation and ataxia that involves defects in the lysosomal transport of sialic acid. Leppänen et al., 1996, Genomics 37:62-67 (Leppänen) located the gene for Salla disease in the immediate vicinity of the marker D6S280. Leppänen screened a PAC library with the marker D6S280 and obtained three positive clones, among which were PAC 141B1 and PAC 224H23, strongly suggesting that the gene for Salla disease is present on these PACs.

SUMMARY OF THE INVENTION

The present invention is directed to novel human DNA sequences encoding a voltage-gated potassium channel, KCNQ5, located in a chromosomal region that contains a gene associated with Stargardt-like macular dystrophy, cone-rod macular dystrophy, and Salla disease.

The present invention includes genomic KCNQ5 DNA as well as cDNA that encodes the KCNQ5 protein. The human genomic KCNQ5 DNA is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:1. The human cDNA encoding KCNQ5 protein is substantially free from other nucleic acids and has the nucleotide sequence shown in SEQ.ID.NO.:2. Also provided is KCNQ5 protein encoded by the novel DNA sequences. The human KCNQ5 protein is substantially free from other proteins and has the amino acid sequence shown in SEQ.ID.NO.:3. Methods of expressing KCNQ5 protein in recombinant systems are provided as well as methods of identifying activators and inhibitors of KCNQ5 protein function. Also provided are diagnostic methods that detect carriers of mutant KCNQ5 genes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-AO shows the genomic DNA sequence of human KCNQ5 (SEQ.ID.NO.:1). Underlined nucleotides in capitals represent exons. The start ATG codon in exon 1 and the stop TAA codon in exon 14 are shown in bold italics. The D6D280 genetic marker and a phosphoglycerate pseudogene are underlined in bold. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, and 13 and 14 are unknown. These gaps are represented as runs of ten bold ns for the sake of convenience.

Figure 2A-E shows the nucleotide sequence (SEQ.ID.NO.:2) and encoded amino acid sequence (SEQ.ID.NO.:3) of human KCNQ5 cDNA. The ATG start codon is at position 138; the TAA stop codon is at position 2,676.

Figure 3A shows the results of a Northern blot of KCNQ5 mRNA expression in various human tissues. Figure 3B shows the results of RT-PCR analysis of KCNQ5 mRNA expression in various human tissues.

Figure 4A shows a sequence alignment of human KCNQ5 protein (SEQ.ID.NO.:3) with human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:5). Figure 4B-C shows a multiple sequence alignment between human KCNQ5 protein (SEQ.ID.NO.:3), human KCNQ1 protein (SEQ.ID.NO.:43), human KCNQ2 protein (SEQ.ID.NO.:6), human KCNQ3 protein (SEQ.ID.NO.:7), and human KCNQ4 protein (SEQ.ID.NO.:4). The consensus sequence shown is (SEQ.ID.NO.:8).

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of this invention:

"Substantially free from other proteins" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other proteins. Thus, a KCNQ5 protein preparation that is substantially free from other proteins will contain, as a percent of its total protein, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 proteins. Whether a given KCNQ5 protein preparation is substantially free from other proteins can be determined by such conventional techniques of assessing protein purity as, *e.g.*, sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) combined with appropriate detection methods, *e.g.*, silver staining or immunoblotting.

"Substantially free from other nucleic acids" means at least 90%, preferably 95%, more preferably 99%, and even more preferably 99.9%, free of other nucleic acids. Thus, a KCNQ5 DNA preparation that is substantially free from other nucleic acids will contain, as a percent of its total nucleic acid, no more than 10%, preferably no more than 5%, more preferably no more than 1%, and even more preferably no more than 0.1%, of non- KCNQ5 nucleic acids. Whether a given KCNQ5 DNA preparation is substantially free from other nucleic acids can be determined by such conventional techniques of assessing nucleic acid purity as, *e.g.*, agarose gel electrophoresis combined with appropriate staining methods, *e.g.*, ethidium bromide staining, or by sequencing.

A "conservative amino acid substitution" refers to the replacement of one amino acid residue by another, chemically similar, amino acid residue. Examples of such conservative substitutions are: substitution of one hydrophobic residue (isoleucine, leucine, valine, or methionine) for another; substitution of one polar residue for another polar residue of the same charge (*e.g.*, arginine for lysine; glutamic acid for aspartic acid); substitution of one aromatic amino acid (tryptophan, tyrosine, or phenylalanine) for another.

A polypeptide has "substantially the same biological activity as KCNQ5" if that polypeptide conducts a voltage-gated potassium current when expressed in appropriate cell types and has an amino acid sequence that is at least about 50% identical to SEQ.ID.NO.:3 when measured by such standard programs as BLAST or FASTA.

The present invention relates to the identification and cloning of KCNQ5, a gene encoding a novel voltage-gated potassium channel. The human KCNQ5 gene is located on chromosome 6q14, in a chromosomal region that contains genes that have been linked with the occurrence of at least three diseases: Stargardt-like macular dystrophy, cone-rod dystrophy, and Salla disease.

The human KCNQ5 gene is present on PAC clones from chromosomal region 6q14. PAC141B1 was sequenced and KCNQ5 was found based on homology between the genomic sequences of KCNQ5 present in PAC 141B1 and the sequences of known potassium channel genes. PAC 141B1 is available from Research Genetics, Inc., Huntsville, AL, as an individual clone from the RPCI4,5,6 Library (catalog number CTLI.C). Using PCR primers derived from the KCNQ5 sequence, a cDNA sequence representing the coding region as well as a large portion of the 3'-UTR of KCNQ5 was isolated from a human fetal brain cDNA library. Comparison of this cDNA clone with the genomic sequences present in PAC141B1, as well as KCNQ5 sequences found in PAC224H23, showed that exons 3-11 and portions of flanking intronic regions are present in PAC141B1. Exon 2 and flanking intronic regions were found in PAC224H23, while the rest of the KCNQ5 gene (exons 1, 12-14, and flanking intronic regions) was recovered from total human genomic DNA by using cDNA primers and a GenomeWalker kit from Clontech, Palo Alto, CA.

PAC141B1 and PAC224H23 are located in the region of the Salla disease gene (Leppänen et al., 1996, Genomics 37:62-67). PAC141B1 contains the polymorphic genetic marker D6S280 that is located in intron 3 of the KCNQ5 gene between exons 3 and 4 (Figure 1). D6S280 is the marker that detects the maximum LOD score of 5.5 (at genetic distance = 0) in families with Stargardt-like macular dystrophy (Stone et al., Arch. Ophthalmol. 112:765-772). D6S280 also detects a LOD score of 3.31 (at genetic distance = 0) in families with cone-rod dystrophy (Kelsell et al., 1998, Am. J. Hum. Genet. 63:274-279). These LOD scores indicate that D6S280 is very closely linked to, and probably is within, the gene for Stargardt-like macular dystrophy and cone-rod dystrophy. In view of these findings, it is likely that KCNQ5 is involved in Salla disease, Stargardt-like macular dystrophy, and cone-rod dystrophy.

That KCNQ5 should be involved with these three diseases is consistent with its expression pattern (see Figure 3A-B) which shows that KCNQ5 is expressed predominately in the retina and brain, in addition to being expressed in the

skeletal muscle. Stargardt-like macular dystrophy and cone-rod dystrophy are inherited retinal diseases while Salla disease is a disorder that is characterized by early onset psychomotor retardation and ataxia.

Bioinformatic analysis revealed a striking homology of the KCNQ5 protein to a group of voltage gated potassium channels (KCNQ1, KCNQ2, KCNQ3, and KCNQ4; see Figure 4A-B). All of the typical amino acid motifs of these potassium channels are preserved in KCNQ5. A Kyte-Doolittle algorithm analysis predicts a transmembrane organization for KCNQ5 that is typical for this group of potassium channels. Mutations in members of this family of potassium channels have been shown to result in inherited disease (KCNQ2 and KCNQ3, epilepsy [Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690]; KCNQ4, a form of nonsyndromic dominant deafness [Kubisch et al., 1999, Cell 96:437-446], KCNQ1, congenital long QT syndrome which causes cardiac arrhythmias and sudden death [Splawski et al., 1997, N. Engl. J. Med. 336:1562-1567]).

The present invention provides DNA encoding KCNQ5 that is substantially free from other nucleic acids. The present invention also provides recombinant DNA molecules encoding KCNQ5. The present invention provides DNA molecules substantially free from other nucleic acids comprising the nucleotide sequence shown in Figure 1 as SEQ.ID.NO.:1. Analysis of SEQ.ID.NO.:1 revealed that this genomic sequence defines a gene having 14 exons. These exons collectively have an open reading frame that encodes a protein of 846 amino acids.

The present invention includes cDNA encoding KCNQ5 protein. Such a cDNA is shown in Figure 2 as SEQ.ID.NO.:2. The present invention therefore includes DNA comprising the nucleotide sequence SEQ.ID.NO.:2. The DNA can be isolated or substantially free of other DNA sequences.

The present invention includes DNA molecules substantially free from other nucleic acids comprising the coding region of SEQ.ID.NO.:2. Accordingly, the present invention includes DNA molecules substantially free from other nucleic acids having a sequence comprising positions 138-2,675 of SEQ.ID.NO.:2. Also included are recombinant DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2 and isolated DNA molecules having a nucleotide sequence comprising positions 138-2,675 of SEQ.ID.NO.:2.

The novel DNA sequences of the present invention encoding KCNQ5, in whole or in part, can be linked with other DNA sequences, *i.e.*, DNA sequences to which KCNQ5 is not naturally linked, to form "recombinant DNA molecules" encoding KCNQ5. Such other sequences can include DNA sequences that control transcription or translation such as, *e.g.*, translation initiation sequences, promoters for RNA polymerase II, transcription or translation termination sequences, enhancer sequences, sequences that control replication in microorganisms, sequences that confer antibiotic resistance, or sequences that encode a polypeptide "tag" such as, *e.g.*, a polyhistidine tract or the myc epitope. The novel DNA sequences of the present invention can be inserted into vectors such as plasmids, cosmids, viral vectors, P1 artificial chromosomes, or yeast artificial chromosomes.

Included in the present invention are DNA sequences that hybridize to at least one of SEQ.ID.NO:1 or SEQ.ID.NO:2 under stringent conditions. By way of example, and not limitation, a procedure using conditions of high stringency is as follows: Prehybridization of filters containing DNA is carried out for 2 hr. to overnight at 65°C in buffer composed of 6X SSC, 5X Denhardt's solution, and 100 μg/ml denatured salmon sperm DNA. Filters are hybridized for 12 to 48 hrs at 65°C in prehybridization mixture containing 100 μg/ml denatured salmon sperm DNA and 5-20 X 10^6 cpm of ^{32}P-labeled probe. Washing of filters is done at 37°C for 1 hr in a solution containing 2X SSC, 0.1% SDS. This is followed by a wash in 0.1X SSC, 0.1% SDS at 50°C for 45 min. before autoradiography.

Other procedures using conditions of high stringency would include either a hybridization carried out in 5XSSC, 5X Denhardt's solution, 50% formamide at 42°C for 12 to 48 hours or a washing step carried out in 0.2X SSPE, 0.2% SDS at 65°C for 30 to 60 minutes.

Reagents mentioned in the foregoing procedures for carrying out high stringency hybridization are well known in the art. Details of the composition of these reagents can be found in, *e.g.*, Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press. In addition to the foregoing, other conditions of high stringency which may be used are well known in the art.

The degeneracy of the genetic code is such that, for all but two amino acids, more than a single codon encodes a particular amino acid. This allows for the construction of synthetic DNA that encodes the KCNQ5 protein where the nucleotide

sequence of the synthetic DNA differs significantly from the nucleotide sequences of SEQ.ID.NO:2, but still encodes the same KCNQ5 protein as SEQ.ID.NO:2. Such synthetic DNAs are intended to be within the scope of the present invention.

Mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:1 or SEQ.ID.NO:2 which give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

Another aspect of the present invention includes host cells that have been engineered to contain and/or express DNA sequences encoding KCNQ5 protein. Such recombinant host cells can be cultured under suitable conditions to produce KCNQ5 protein. An expression vector containing DNA encoding KCNQ5 protein can be used for expression of KCNQ5 protein in a recombinant host cell. Recombinant host cells may be prokaryotic or eukaryotic, including but not limited to, bacteria such as *E. coli*, fungal cells such as yeast, mammalian cells including, but not limited to, cell lines of human, bovine, porcine, monkey and rodent origin, amphibian cells such as *Xenopus* oocytes, and insect cells including but not limited to *Drosophila* and silkworm derived cell lines. Cells and cell lines which are suitable for recombinant expression of KCNQ5 protein and which are widely mavailable, include but are not limited to, L cells L-M(TK$^-$) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), ARPE-19 human retinal pigment epithelium (ATCC CRL-2302), *Xenopus* melanophores, and *Xenopus* oocytes.

A variety of mammalian expression vectors can be used to express recombinant KCNQ5 in mammalian cells. Commercially available mammalian expression vectors which are suitable include, but are not limited to, pMC1neo (Stratagene), pSG5 (Stratagene), pcDNAI and pcDNAIamp, pcDNA3, pcDNA3.1, pCR3.1 (Invitrogen), EBO-pSV2-neo (ATCC 37593), pBPV-1(8-2) (ATCC 37110), pdBPV-MMTneo(342-12) (ATCC 37224), pRSVgpt (ATCC 37199), pRSVneo (ATCC 37198), and pSV2-dhfr (ATCC 37146). Another suitable vector is the PT7TS oocyte expression vector. Following expression in recombinant cells, KCNQ5 can

be purified by conventional techniques to a level that is substantially free from other proteins.

Certain voltage-gated potassium channel subunits have been found to require the expression of other voltage-gated potassium channel subunits as "chaperones" in order to be properly expressed at high levels and inserted in membranes. For example, co-expression of KCNQ3 appears to enhance the expression of KCNQ2 in *Xenopus* oocytes (Wang et al., 1998, Science 282:1890-1893). Also, some voltage-gated potassium channel Kv1α subunits require other related alpha subunits or Kvβ2 subunits (Shi et al., 1995, Neuron 16:843-852). Accordingly, the recombinant expression of the KCNQ5 protein may under certain circumstances benefit from the co-expression of other voltage-gated potassium channel proteins and such co-expression is intended to be within the scope of the present invention.

The present invention includes KCNQ5 protein substantially free from other proteins. The amino acid sequence of the full-length KCNQ5 protein is shown in Figure 2 as SEQ.ID.NO.:3. Thus, the present invention includes KCNQ5 protein substantially free from other proteins having the amino acid sequence SEQ.ID.NO.:3. The present invention also includes isolated KCNQ5 protein having the amino acid sequence SEQ.ID.NO.:3.

Mutated forms of KCNQ5 proteins are intended to be within the scope of the present invention. In particular, mutated forms of SEQ.ID.NO:3 that give rise to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration are within the scope of the present invention.

As with many proteins, it is possible to modify many of the amino acids of KCNQ5 and still retain substantially the same biological activity as the original protein. Thus, the present invention includes modified KCNQ5 proteins which have amino acid deletions, additions, or substitutions but that still retain substantially the same biological activity as KCNQ5. It is generally accepted that single amino acid substitutions do not usually alter the biological activity of a protein (see, *e.g.*, Molecular Biology of the Gene, Watson *et al.*, 1987, Fourth Ed., The Benjamin/Cummings Publishing Co., Inc., page 226; and Cunningham & Wells, 1989, Science 244:1081-1085). Accordingly, the present invention includes polypeptides where one amino acid substitution has been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as

KCNQ5. The present invention also includes polypeptides where two or more amino acid substitutions have been made in SEQ.ID.NO:3 wherein the polypeptides still retain substantially the same biological activity as KCNQ5. In particular, the present invention includes embodiments where the above-described substitutions are conservative substitutions. In particular, the present invention includes embodiments where the above-described substitutions do not occur in positions where the amino acid present in KCNQ5 is also present in the corresponding position of any one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4 (see Figure 4A-B).

The KCNQ5 proteins of the present invention may contain post-translational modifications, *e.g.*, covalently linked carbohydrate, phosphorylation, myristoylation, *etc.*.

The present invention also includes chimeric KCNQ5 proteins. Chimeric KCNQ5 proteins consist of a contiguous polypeptide sequence of at least a portion of KCNQ5 protein fused to a polypeptide sequence of a non-KCNQ5 protein.

The present invention also includes isolated forms of KCNQ5 proteins and KCNQ5 DNA. Use of the term "isolated" indicates that KCNQ5 protein or KCNQ5 DNA has been removed from its normal cellular environment. Thus, an isolated KCNQ5 protein may be in a cell-free solution or placed in a different cellular environment from that in which it occurs naturally. The term isolated does not imply that an isolated KCNQ5 protein is the only protein present. but instead means that an isolated KCNQ5 protein is at least 95% free of non-amino acid material (*e.g.*, nucleic acids, lipids, carbohydrates) naturally associated with the KCNQ5 protein. Thus, a KCNQ5 protein that is expressed in bacteria or even in eukaryotic cells which do not naturally (*i.e.*, without human intervention) express it through recombinant means is an "isolated KCNQ5 protein."

It is known that other members of the family of potassium channels to which KCNQ5 belongs can interact to form heteromeric structures resulting in functional potassium channels. For example, KCNQ2 and KCNQ3 can assemble to form a heteromeric functional potassium channel (Wang et al., 1998, Science 282:1890-1893). Accordingly, it is believed likely that KCNQ5 will also be able to form heteromeric structures with other proteins where such heteromeric structures constitute functional potassium channels. Thus, the present invention includes such heteromers comprising KCNQ5. Preferred heteromers are those in which KCNQ5 forms heteromers with at least one of KCNQ1, KCNQ2, KCNQ3, or KCNQ4.

A cDNA fragment encoding full-length KCNQ5 can be isolated from a human retinal or brain cDNA library by using the polymerase chain reaction (PCR) employing suitable primer pairs. Such primer pairs can be selected based upon the cDNA sequence for KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2. Suitable primer pairs would be, *e.g.*:

5'-GGGGGCCCGGATGAGCC-3' (SEQ.ID.NO.:9) and

5'-GAAGAACTTATTTCAGTTTGA-3' (SEQ.ID.NO.:10)

The above primers are meant to be illustrative only; one skilled in the art would readily be able to design other suitable primers based upon SEQ.ID.NO.:2. Such primers could be produced by methods of oligonucleotide synthesis that are well known in the art.

PCR reactions can be carried out with a variety of thermostable enzymes including but not limited to AmpliTaq, AmpliTaq Gold, or Vent polymerase. For AmpliTaq, reactions can be carried out in 10 mM Tris-Cl, pH 8.3, 2.0 mM $MgCl_2$, 200 μM for each dNTP, 50 mM KCl, 0.2 μM for each primer, 10 ng of DNA template, 0.05 units/μl of AmpliTaq. The reactions are heated at 95°C for 3 minutes and then cycled 35 times using the cycling parameters of 95°C, 20 seconds, 62°C, 20 seconds, 72°C, 3 minutes. In addition to these conditions, a variety of suitable PCR protocols can be found in <u>PCR Primer, A Laboratory Manual</u>, edited by C.W. Dieffenbach and G.S. Dveksler, 1995, Cold Spring Harbor Laboratory Press; or <u>PCR Protocols: A Guide to Methods and Applications</u>, Michael *et al.*, eds., 1990, Academic Press .

A suitable cDNA library from which a clone encoding KCNQ5 can be isolated would be Human Retina 5'-stretch cDNA library in lambda gt10 or lambda gt11 vectors (catalog numbers HL1143a and HL1132b, Clontech, Palo Alto, CA) or human fetal brain 5-stretch plus cDNA library (catalog number HL5024t, Clontech, Palo Alto, CA). The primary clones of such a library can be subdivided into pools with each pool containing approximately 20,000 clones and each pool can be amplified separately.

By this method, a cDNA fragment encoding an open reading frame of 846 amino acids (SEQ.ID.NO.:3) can be obtained. This cDNA fragment can be cloned into a suitable cloning vector or expression vector. For example, the fragment can be cloned into the mammalian expression vector pcDNA3.1 (Invitrogen, San Diego, CA). KCNQ5 protein can then be produced by transferring an expression

vector encoding KCNQ5 or portions thereof into a suitable host cell and growing the host cell under appropriate conditions. KCNQ5 protein can then be isolated by methods well known in the art.

As an alternative to the above-described PCR method, a cDNA clone encoding KCNQ5 can be isolated from a cDNA library using as a probe oligonucleotides specific for KCNQ5 and methods well known in the art for screening cDNA libraries with oligonucleotide probes. Such methods are described in, *e.g.*, Sambrook *et al.*, 1989, *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Glover, D.M. (ed.), 1985, *DNA Cloning: A Practical Approach*, MRL Press, Ltd., Oxford, U.K., Vol. I, II. Oligonucleotides that are specific for KCNQ5 and that can be used to screen cDNA libraries can be readily designed based upon the cDNA sequence of KCNQ5 shown in Figure 2 as SEQ.ID.NO.:2 and can be synthesized by methods well-known in the art.

Genomic clones containing the KCNQ5 gene can be obtained from commercially available human PAC or BAC libraries available from Research Genetics, Huntsville, AL. PAC clones containing the KCNQ5 gene (*e.g.*, PAC141B1, PAC224H23) are commercially available from Research Genetics, Huntsville, AL (catalog number for individual PAC clones is RPCI.C). Alternatively, one may prepare genomic libraries, especially in P1 artificial chromosome vectors, from which genomic clones containing the KCNQ5 can be isolated, using probes based upon the KCNQ5 sequences disclosed herein. Methods of preparing such libraries are known in the art (Ioannou *et al.*,1994, Nature Genet. 6:84-89).

The novel DNA sequences of the present invention can be used in various diagnostic methods relating to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. The present invention provides diagnostic methods for determining whether a patient carries a mutation in the KCNQ5 gene that predisposes that patient toward the development of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In broad terms, such methods comprise determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not suffer from Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the

patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Such methods of diagnosis may be carried out in a variety of ways. For example, one embodiment comprises:

(a) providing PCR primers from a region of the KCNQ5 gene;

(b) performing PCR on a DNA sample from the patient to produce a PCR fragment from the patient;

(c) performing PCR on a control DNA sample comprising a nucleotide sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2 to produce a control PCR fragment;

(d) determining the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment;

(e) comparing the nucleotide sequence of the PCR fragment from the patient to the nucleotide sequence of the control PCR fragment;

where a difference between the nucleotide sequence of the PCR fragment from the patient and the nucleotide sequence of the control PCR fragment indicates that the patient has a mutation in the KCNQ5 gene and thus is likely to have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the PCR primers are from a region of the KCNQ5 gene where it is suspected that a patient harbors a mutation. In a particular embodiment, the PCR primers are from the coding region of the KCNQ5 gene, *i.e.*, from the coding region of SEQ.ID.NO:1 or SEQ.ID.NO:2. In a particular embodiment, the PCR primers amplify a region that includes the marker D6S280.

In a particular embodiment, the DNA sample from the patient is cDNA that has been prepared from an RNA sample from the patient. In another embodiment, the DNA sample from the patient is genomic DNA. In a particular embodiment, the control DNA sample is DNA from a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are determined by DNA sequencing.

In a particular embodiment, the nucleotide sequences of the PCR fragment from the patient and the control PCR fragment are compared by direct comparison after DNA sequencing. In another embodiment, step (d) is omitted and the comparison in step (e) is made by a process that includes hybridizing the PCR fragment from the patient and the control PCR fragment and then using an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly. Such an endonuclease is, *e.g.*, S1. In this embodiment, the conversion of the PCR fragment from the patient to smaller fragments after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene. In such embodiments, it may be advantageous to label (radioactively, enzymatically, immunologically, *etc.*) the PCR fragment from the patient or the control PCR fragment.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) obtaining an RNA sample from the patient;

(b) performing reverse transcription-PCR (RT-PCR) on the RNA sample using primers that span a region of the coding sequence of the KCNQ5 gene to produce a PCR fragment from the patient where the PCR fragment from the patient has a defined length, the length being dependent upon the identity of the primers that were used in the RT-PCR;

(c) hybridizing the PCR fragment to DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or to portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels, to form a hybrid;

(d) treating the hybrid produced in step (c) with an endonuclease that cleaves at any mismatched positions in the hybrid but does not cleave the hybrid if the two fragments match perfectly;

(e) determining whether the endonuclease cleaved the hybrid by determining the length of the PCR fragment from the patient after endonuclease treatment where a reduction in the length of the PCR fragment from the patient after endonuclease treatment indicates that the patient carries a mutation in the KCNQ5 gene.

In a variation of the above-described method, instead of determining the length of the PCR fragment from the patient after endonuclease treatment, the

length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels is determined after endonuclease treatment. In such a variation, a reduction in the length of the DNA comprising a sequence selected from the group consisting of SEQ.ID.NO:1 and SEQ.ID.NO.:2, or the DNA comprising portions of SEQ.ID.NO:1 or SEQ.ID.NO.:2 that are sufficiently long to give rise to bands that can be seen on polyacrylamide gels indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) making cDNA from an RNA sample from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the cDNA to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention provides a method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) preparing genomic DNA from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the genomic DNA to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

The present invention also provides oligonucleotide probes, based upon the sequences of SEQ.ID.NO:1 or SEQ.ID.NO:2, that can be used in diagnostic methods related to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In particular, the present invention includes DNA oligonucleotides comprising at least about 10, 15, or 18 contiguous nucleotides of a sequence selected from the group consisting of: SEQ.ID.NO:1 and SEQ.ID.:NO.2 where the oligonucleotide probe comprises no stretch of contiguous nucleotides longer than 5 of a sequence selected from the group consisting of: SEQ.ID.NO:1 and SEQ.ID.:NO.2 other than the said at least about 10, 15, or 18 contiguous nucleotides. The oligonucleotides can be substantially free from other nucleic acids. Also provided by the present invention are corresponding RNA oligonucleotides. The DNA or RNA oligonucleotide probes can be packaged in kits.

In addition to the diagnostic utilities described above, the present invention makes possible the recombinant expression of the KCNQ5 protein in various cell types. Such recombinant expression makes possible the study of this protein so that its biochemical activity and its role in Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration can be elucidated.

The present invention also makes possible the development of assays which measure the biological activity of the KCNQ5 protein. Such assays using recombinantly expressed KCNQ5 protein are especially of interest. Assays for KCNQ5 protein activity can be used to screen libraries of compounds or other sources of compounds to identify compounds that are activators or inhibitors of the activity of KCNQ5 protein. Such identified compounds can serve as "leads" for the development of pharmaceuticals that can be used to treat patients having Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. In versions of the above-described assays, mutant KCNQ5 proteins are used and inhibitors or activators of the activity of the mutant KCNQ5 proteins are identified.

Preferred cell lines for recombinant expression of KCNQ5 are those which do not express endogenous potassium channels (*e.g.*, CV-1, NIH-3T3). Such

cell lines can be loaded with ^{86}Rb, an ion which can pass through potassium channels. The ^{86}Rb-loaded cells can be exposed to collections of substances (*e.g.*, combinatorial libraries, natural products) and those substances that are able to alter ^{86}Rb efflux identified. Such substances are likely to be activators or inhibitors of KCNQ5.

The present invention includes a method of identifying activators or inhibitors of KCNQ5 comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

(b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

In particular embodiments, the biological activity is the production of a voltage-gated potassium current, or efflux of ^{86}Rb.

In particular embodiments, a vector encoding KCNQ5 is transferred into *Xenopus* oocytes in order to cause the expression of KCNQ5 protein in the oocytes. Alternatively, RNA encoding KCNQ5 protein can be prepared *in vitro* and injected into the oocytes, also resulting in the expression of KCNQ5 protein in the oocytes. Following expression of KCNQ5 in the oocytes, membrane currents are measured after the transmembrane voltage is changed in steps. A change in membrane current is observed when the KCNQ5 channels opens, allowing potassium ion flow. Similar oocytes studies were reported for KCNQ2 and KCNQ3 potassium channels in Wang et al., 1998, Science 282:1890-1893.

Inhibitors of KCNQ5 can be identified by exposing the oocytes expressing KCNQ5 to collections of substances and determining whether the substances can block or diminish the membrane currents observed in the absence of the substance.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b);

where if the potassium membrane currents measured in step (c) are greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

The present invention also includes assays for the identification of activators and inhibitors of KCNQ5 that are based upon FRET between a first and a second fluorescent dye where the first dye is bound to one side of the plasma membrane of a cell expressing KCNQ5 and the second dye is free to shuttle from one face of the membrane to the other face in response to changes in membrane potential. In certain embodiments, the first dye is impenetrable to the plasma membrane of the cells and is bound predominately to the extracellular surface of the plasma membrane. The second dye is trapped within the plasma membrane but is free to diffuse within the membrane. At normal (*i.e.*, negative) resting potentials of the membrane, the second dye is bound predominately to the inner surface of the extracellular face of the plasma membrane, thus placing the second dye in close proximity to the first dye. This close proximity allows for the generation of a large amount of FRET between the two dyes. Following membrane depolarization, the second dye moves from the extracellular face of the membrane to the intracellular face, thus increasing the distance between the dyes. This increased distance results in a decrease in FRET, with a corresponding increase in fluorescent emission derived from the first dye and a corresponding decrease in the fluorescent emission from the second dye. See figure 1 of González & Tsien, 1997, Chemistry & Biology 4:269-277. See also González & Tsien, 1995, Biophys. J. 69:1272-1280 and U.S. Patent No. 5,661,035.

In certain embodiments, the first dye is a fluorescent lectin or a fluorescent phospholipid that acts as the fluorescent donor. Examples of such a first dye are: a coumarin-labeled phosphatidylethanolamine (*e.g.*, N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-ethanolamine) or N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); a fluorescently-labeled lectin (*e.g.*, fluorescein-labeled wheat germ agglutinin). In certain embodiments, the second dye is an oxonol that acts as the fluorescent acceptor. Examples of such a second dye are: bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols (*e.g.*, bis(1,3-dihexyl-2-

thiobarbiturate)trimethineoxonol) or pentamethineoxonol analogues (*e.g.*, bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; or bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol). See González & Tsien, 1997, Chemistry & Biology 4:269-277 for methods of synthesizing various dyes suitable for use in the present invention. In certain embodiments, the assay may comprise a natural carotenoid, *e.g.*, astaxanthin, in order to reduce photodynamic damage due to singlet oxygen.

The above described assays can be utilized to discover activators and inhibitors of KCNQ5. Such assays will generally utilize cells that express KCNQ5, *e.g.*, by transfection with expression vectors encoding KCNQ5. In assays for inhibitors, such cells will generally have a resting membrane potential that is roughly equal to the threshhold for activation of the KCN5Q channel. This is because most untransfected cells will have membrane potentials that are depolarized relative to the threshhold potential of KCNQ5 channels. Therefore, when KCNQ5 is expressed in these cells, the KCNQ5 channels open. This lets K+ out of the cells, which tends to hyperpolarize the membrane potential. This closes some of the KCNQ5 channels, leading to relative depolarization. In this way, a steady state develops around the threshhold for activation of the KCNQ5 channel. Inhibitors of KCNQ5 will, therefore, disturb this steady state and depolarize the cell. In assays for activators, KCNQ5 will be transfected into a cell line that also expresses a counteracting, depolarizing current. The membrane potential in these cells will therefore be set by contributions of both the KCNQ5 channel and the endogenous depolarizing current, resulting in a more depolarized resting potential. Ideally, the endogenous current will play the major role in the absence of a KCNQ5 activator. Activators of KCNQ5 will open this channel and increase the contribution of KCNQ5 to the membrane potential relative to the other current and the potential will, therefore, hyperpolarize in response to an activator of KCNQ5. Changes in membrane potential (depolarizations and hyperpolarizations) that are caused by activators and inhibitors of KCNQ5 can be monitored by the assays using FRET described above.

Accordingly, the present invention provides a method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

The present invention also provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

In a variation of the assay described above, instead of the transfected cell's membrane potential being allowed to reach steady state on its own, the membrane potential is artificially set at a potential in which the KCNQ5 channel is open. This can be done, *e.g.*, by variation of the external K+ concentration in a known manner (*e.g.*, increased concentrations of external K+). If such cells, having open KCNQ5 channels, are exposed to inhibitors of KCNQ5, the KCNQ5 channels will close, and the cells' membrane potentials will be depolarized. This depolarization can be observed as a decrease in FRET.

Accordingly, the present invention provides a method of identifying inhibitors of KCNQ5 comprising:

(a) providing cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) adjusting the membrane potential of the cells such that the ion channel formed by KCNQ5 is open;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells;

(d) repeating step (b) and step (c) while the cells are exposed to a substance that is suspected of being an inhibitor of KCNQ5;

where if the amount of FRET exhibited by the cells that are exposed to the substance is less than the amount of FRET exhibited by the cells that have not been exposed to the substance, then the substance is an inhibitor of KCNQ5.

In particular embodiments of the above-described methods, the expression vectors are transfected into the test cells.

In particular embodiments of the above-described methods, KCNQ5 has an amino acid sequence of SEQ.ID.NO.:3.

In particular embodiments of the above-described methods, the first fluorescent dye is selected from the group consisting of: a fluorescent lectin; a fluorescent phospholipid; a coumarin-labeled phosphatidylethanolamine; N-(6-chloro-7-hydroxy-2-oxo-2H--1-benzopyran-3-carboxamidoacetyl)-dimyristoylphosphatidyl-ethanolamine); N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)-dipalmitoylphosphatidylethanolamine); and fluorescein-labeled wheat germ agglutinin.

In particular embodiments of the above-described methods, the second fluorescent dye is selected from the group consisting of: an oxonol that acts as the fluorescent acceptor; bis(1,3-dialkyl-2-thiobarbiturate)trimethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)trimethineoxonol; bis(1,3-dialkyl-2-thiobarbiturate)quatramethineoxonols; bis(1,3-dialkyl-2-thiobarbiturate)pentamethineoxonols; bis(1,3-dihexyl-2-thiobarbiturate)pentamethineoxonol; bis(1,3-dibutyl-2-thiobarbiturate)pentamethineoxonol); and bis(1,3-dialkyl-2-thiobarbiturate)hexamethineoxonols.

In a particular embodiment of the above-described methods, the cells are eukaryotic cells. In another embodiment, the cells are mammalian cells. In other embodiments, the cells are L cells L-M(TK$^-$) (ATCC CCL 1.3), L cells L-M (ATCC CCL 1.2), 293 (ATCC CRL 1573), Raji (ATCC CCL 86), CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3 (ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), *Xenopus* melanophores, or *Xenopus* oocytes.

In particular embodiments of the above-described methods, the control cells do not comprise item (a)(1) but do comprise items (a)(2) and (a)(3).

In assays to identify activators or inhibitors of KCNQ5, it may be advantageous to co-express another potassium channel, *e.g.*, KCNQ1, KCNQ2, KCNQ3, or KCNQ4, together with KCNQ5, or with an accessory subunit, such as the IsK protein or one of its homologues, in order to form a functional heteromeric potassium channel.

While the above-described methods are explicitly directed to testing whether "a" substance is an activator or inhibitor of KCNQ5, it will be clear to one skilled in the art that such methods can be adapted to test collections of substances, *e.g.*, combinatorial libraries, to determine whether any members of such collections are activators or inhibitors of KCNQ5. Accordingly, the use of collections of substances, or individual members of such collections, as the substance in the above-described methods is within the scope of the present invention.

The present invention includes pharmaceutical compositions comprising activators or inhibitors of KCNQ5 protein that have been identified by the herein-described methods. The activators or inhibitors are generally combined with pharmaceutically acceptable carriers to form pharmaceutical compositions. Examples of such carriers and methods of formulation of pharmaceutical compositions containing activators or inhibitors and carriers can be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain a therapeutically effective amount of the activators or inhibitors.

Therapeutic or prophylactic compositions are administered to an individual in amounts sufficient to treat or prevent conditions where KCNQ5 activity is abnormal. The effective amount can vary according to a variety of factors such as the individual's condition, weight, gender, and age. Other factors include the mode of administration. The appropriate amount can be determined by a skilled physician.

Compositions can be used alone at appropriate dosages. Alternatively, co-administration or sequential administration of other agents can be desirable.

The compositions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for administration. For example, the compositions can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they can also be administered in intravenous (both bolus and infusion),

intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

Advantageously, compositions can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. Furthermore, compositions can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dosage regimen utilizing the compositions is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal, hepatic and cardiovascular function of the patient; and the particular composition thereof employed. A physician of ordinary skill can readily determine and prescribe the effective amount of the composition required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentrations of composition within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the composition's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a composition.

The present invention includes a method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration and other forms of macular degeneration, deafness, epilepsy, and different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

When screening compounds in order to identify potential pharmaceuticals that specifically interact with a target ion channel, it is necessary to ensure that the compounds identified are as specific as possible for the target ion channel. To do this, it is necessary to screen the compounds against as wide an array as possible of ion channels that are similar to the target ion channel. Thus, in order to find compounds that are potential pharmaceuticals that interact with ion channel A, it

is not enough to ensure that the compounds interact with ion channel A (the "plus target") and produce the desired pharmacological effect through ion channel A. It is also necessary to determine that the compounds do not interact with ion channels B, C, D, *etc* .(the "minus targets"). In general, as part of a screening program, it is important to have as many minus targets as possible (see Hodgson, 1992, Bio/Technology 10:973-980, at 980). KCNQ5 protein, DNA encoding KCNQ5 protein, and recombinant cells that have been engineered to express KCNQ5 protein have utility in that they can be used as "minus targets" in screens designed to identify compounds that specifically interact with other ion channels. For example, Wang et al., 1998, Science 282:1890-1893 have shown that KCNQ2 and KCNQ3 form a heteromeric potassium ion channel know as the "M-channel." The M-channel is an important target for drug discovery since mutations in KCNQ2 and KCNQ3 are responsible for causing epilepsy (Biervert et al., 1998, Science 279:403-406; Singh et al., 1998, Nature Genet. 18:25-29; Schroeder et al., Nature 1998, 396:687-690). A screening program designed to identify activators or inhibitors of the M-channel would benefit greatly by the use of KCNQ5 as a minus target.

The present invention also includes antibodies to the KCNQ5 protein. Such antibodies may be polyclonal antibodies or monoclonal antibodies. The antibodies of the present invention are raised against the entire KCNQ5 protein or against suitable antigenic fragments of the protein that are coupled to suitable carriers, *e.g.*, serum albumin or keyhole limpet hemocyanin, by methods well known in the art. Methods of identifying suitable antigenic fragments of a protein are known in the art. See, *e.g.*, Hopp & Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828; and Jameson & Wolf, 1988, CABIOS (Computer Applications in the Biosciences) 4:181-186.

For the production of polyclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected on a periodic basis into an appropriate non-human host animal such as, *e.g.*, rabbits, sheep, goats, rats, mice. The animals are bled periodically and sera obtained are tested for the presence of antibodies to the injected antigen. The injections can be intramuscular, intraperitoneal, subcutaneous, and the like, and can be accompanied with adjuvant.

For the production of monoclonal antibodies, KCNQ5 protein or an antigenic fragment, coupled to a suitable carrier, is injected into an appropriate non-human host animal as above for the production of polyclonal antibodies. In the case

of monoclonal antibodies, the animal is generally a mouse. The animal's spleen cells are then immortalized, often by fusion with a myeloma cell, as described in Kohler & Milstein, 1975, Nature 256:495-497. For a fuller description of the production of monoclonal antibodies, see Antibodies: A Laboratory Manual, Harlow & Lane, eds., Cold Spring Harbor Laboratory Press, 1988.

Gene therapy may be used to introduce KCNQ5 polypeptides into the cells of target organs, *e.g.*, the pigmented epithelium of the retina or other parts of the retina. Nucleotides encoding KCNQ5 polypeptides can be ligated into viral vectors which mediate transfer of the nucleotides by infection of recipient cells. Suitable viral vectors include retrovirus, adenovirus, adeno-associated virus, herpes virus, vaccinia virus, lentivirus, and polio virus based vectors. Alternatively, nucleotides encoding KCNQ5 polypeptides can be transferred into cells for gene therapy by non-viral techniques including receptor-mediated targeted transfer using ligand-nucleotide conjugates, lipofection, membrane fusion, or direct microinjection. These procedures and variations thereof are suitable for *ex vivo* as well as *in vivo* gene therapy. Gene therapy with KCNQ5 polypeptides will be particularly useful for the treatment of diseases where it is beneficial to elevate KCNQ5 activity.

The present invention includes processes for cloning orthologues of human KCNQ5 from non-human species. In general, such processes include preparing a PCR primer or a hybridization probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 that can be used to amplify a fragment containing the non-human KCNQ5 (in the case of PCR) from a suitable DNA preparation or to select a cDNA or genomic clone containing the non-human KCNQ5 from a suitable library. A preferred embodiment of this process is a process for cloning the KCNQ5 gene from mouse.

By providing DNA encoding mouse KCNQ5, the present invention allows for the generation of an animal model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration. Such animal models can be generated by making transgenic "knockout" or "knockin" mice containing altered KCNQ5 genes. Knockout mice can be generated in which portions of the mouse KCNQ5 gene have been deleted. Knockin mice can be generated in which mutations that have been shown to lead to Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration when present in the human KCNQ5 gene are introduced into the mouse gene. Such knockout and

knockin mice will be valuable tools in the study of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration and will provide important model systems in which to test potential pharmaceuticals or treatments for Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

Accordingly, the present invention includes a method of producing a mouse model of Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration comprising:

(a) designing PCR primers or an oligonucleotide probe based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2 for use in cloning the mouse KCNQ5 gene;

(b) using the PCR primers or the oligonucleotide probe to clone at least a portion of the mouse KCNQ5 gene, the portion being large enough to use in making a transgenic mouse;

(c) producing a transgenic mouse having at least one copy of the mouse KCNQ5 gene altered from its native state.

Methods of producing knockout and knockin mice are well known in the art. One method involves the use of gene-targeted ES cells in the generation of gene-targeted transgenic knockout mice and is described in, *e.g.*, Thomas et al., 1987, Cell 51:503-512, and is reviewed elsewhere (Frohman et al., 1989, Cell 56:145-147; Capecchi, 1989, Trends in Genet. 5:70-76; Baribault et al., 1989, Mol. Biol. Med. 6:481-492).

Techniques are available to inactivate or alter any genetic region to virtually any mutation desired by using targeted homologous recombination to insert specific changes into chromosomal genes. Generally, use is made of a "targeting vector," *i.e.*, a plasmid containing part of the genetic region it is desired to mutate. By virtue of the homology between this part of the genetic region on the plasmid and the corresponding genetic region on the chromosome, homologous recombination can be used to insert the plasmid into the genetic region, thus disrupting the genetic region. Usually, the targeting vector contains a selectable marker gene as well.

In comparison with homologous extrachromosomal recombination, which occurs at frequencies approaching 100%, homologous plasmid-chromosome recombination was originally reported to only be detected at frequencies between 10^{-6} and 10^{-3} (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395; Smithies et al., 1985, Nature 317: 230-234; Thomas et al., 1986, Cell 44:419-428).

Nonhomologous plasmid-chromosome interactions are more frequent, occurring at levels 10^5-fold (Lin et al., 1985, Proc. Natl. Acad. Sci. USA 82:1391-1395) to 10^2-fold (Thomas et al., 1986, Cell 44:419-428) greater than comparable homologous insertion.

To overcome this low proportion of targeted recombination in murine ES cells, various strategies have been developed to detect or select rare homologous recombinants. One approach for detecting homologous alteration events uses the polymerase chain reaction (PCR) to screen pools of transformant cells for homologous insertion, followed by screening individual clones (Kim et al., 1988, Nucleic Acids Res. 16:8887-8903; Kim et al., 1991, Gene 103:227-233). Alternatively, a positive genetic selection approach has been developed in which a marker gene is constructed which will only be active if homologous insertion occurs, allowing these recombinants to be selected directly (Sedivy et al., 1989, Proc. Natl. Acad. Sci. USA 86:227-231). One of the most powerful approaches developed for selecting homologous recombinants is the positive-negative selection (PNS) method developed for genes for which no direct selection of the alteration exists (Mansour et al., 1988, Nature 336:348-352; Capecchi, 1989, Science 244:1288-1292; Capecchi, 1989, Trends in Genet. 5:70-76). The PNS method is more efficient for targeting genes which are not expressed at high levels because the marker gene has its own promoter. Nonhomologous recombinants are selected against by using the Herpes Simplex virus thymidine kinase (HSV-TK) gene and selecting against its nonhomologous insertion with herpes drugs such as gancyclovir (GANC) or FIAU (1-(2-deoxy 2-fluoro-B-D-arabinofluranosyl)-5-iodouracil). By this counter-selection, the percentage of homologous recombinants in the surviving transformants can be increased.

Other methods of producing transgenic mice involve microinjecting the male pronuclei of fertilized eggs. Such methods are well known in the art.

The following non-limiting examples are presented to better illustrate the invention.

EXAMPLE 1

Identification of the human KCNQ5 gene and cDNA cloning

Construction of Libraries for Shotgun Sequencing from PAC Clones

Bacterial strains containing the KCNQ5 PACs (P1 Artificial Chromosomes) were received from Research Genetics (Huntsville, AL). Cells were streaked on Luria-Bertani (LB) agar plates supplemented with the appropriate antibiotic. A single colony was used to prepare a 5-ml starter culture and then 1-L overnight culture in LB medium. The cells were pelleted by centrifugation and PAC DNA was purified by equilibrium centrifugation in cesium chloride-ethidium bromide gradient (Sambrook, Fritsch, and Maniatis, 1989, Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press). Purified PAC DNA was brought to 50 mM Tris pH 8.0, 15 mM $MgCl_2$, and 25% glycerol in a volume of 2 ml and placed in a AERO-MIST nebulizer (CIS-US, Bedford, MA). The nebulizer was attached to a nitrogen gas source and the DNA was randomly sheared at 10 psi for 30 sec. The sheared DNA was ethanol precipitated and resuspended in TE (10 mM Tris, 1 mM EDTA). The ends were made blunt by treatment with Mung Bean Nuclease (Promega, Madison, WI) at 30°C for 30 min, followed by phenol/chloroform extraction, and treatment with T4 DNA polymerase (GIBCO/BRL, Gaithersburg, MD) in multicore buffer (Promega, Madison, WI) in the presence of 40 uM dNTPs at 16°C. To facilitate subcloning of the DNA fragments, BstX I adapters (Invitrogen, Carlsbad, CA) were ligated to the fragments at 14°C overnight with T4 DNA ligase (Promega, Madison, WI). Adapters and DNA fragments less than 500 bp were removed by column chromatography using a cDNA sizing column (GIBCO/BRL, Gaithersburg, MD) according to the instructions provided by the manufacturer. Fractions containing DNA greater than 1 kb were pooled and concentrated by ethanol precipitation. The DNA fragments containing BstX I adapters were ligated into the BstX I sites of pSHOT II which was constructed by subcloning the BstX I sites from pcDNA II (Invitrogen, Carlsbad, CA) into the BssH II sites of pBlueScript (Stratagene, La Jolla, CA). pSHOT II was prepared by digestion with BstX I restriction endonuclease and purified by agarose gel electrophoresis. The gel purified vector DNA was extracted from the agarose by following the Prep-A-Gene (BioRad, Richmond, CA) protocol. To reduce ligation of

the vector to itself, the digested vector was treated with calf intestinal phosphatase (GIBCO/BRL, Gaithersburg, MD. Ligation reactions of the DNA fragments with the cloning vector were transformed into ultra-competent XL-2 Blue cells (Stratagene, La Jolla, CA), and plated on LB agar plates supplemented with 100 μg/ml ampicillin. Individual colonies were picked into a 96 well plate containing 100 μl/well of LB broth supplemented with ampicillin and grown overnight at 37°C. Approximately 25 μl of 80% sterile glycerol was added to each well and the cultures stored at -80°C.

Preparation of plasmid DNA

Glycerol stocks were used to inoculate 5 ml of LB broth supplemented with 100 μg/ml ampicillin either manually or by using a Tecan Genesis RSP 150 robot (Tecan AG, Hombrechtikon, Switzerland) programmed to inoculate 96 tubes containing 5 ml broth from the 96 wells. The cultures were grown overnight at 37°C with shaking to provide aeration. Bacterial cells were pelleted by centrifugation , the supernatant decanted, and the cell pellet stored at -20°C. Plasmid DNA was prepared with a QIAGEN Bio Robot 9600 (QIAGEN, Chatsworth, CA) according to the Qiawell Ultra protocol. To test the frequency and size of inserts, plasmid DNA was digested with the restriction endonuclease Pvu II. The size of the restriction endonuclease products was examined by agarose gel electrophoresis with the average insert size being 1 to 2 kb.

DNA Sequence Analysis of Shotgun clones

DNA sequence analysis was performed using the ABI PRISM™ dye terminator cycle sequencing ready reaction kit with AmpliTaq DNA polymerase, FS (Perkin Elmer, Norwalk, CT). DNA sequence analysis was performed with M13 forward and reverse primers. Following amplification in a Perkin-Elmer 9600, the extension products were purified and analyzed on an ABI PRISM 377 automated sequencer (Perkin Elmer, Norwalk, CT). Approximately 4 sequencing reactions were performed per kb of DNA to be examined (384 sequencing reactions per each of nine PACs).

Assembly of DNA sequences

Phred/Phrap was used for DNA sequences assembly. This program was developed by Dr. Phil Green and licensed from the University of Washington

(Seattle, WA). Phred/Phrap consists of the following programs: Phred for base-calling, Phrap for sequence assembly, Crossmatch for sequence comparisons, Consed and Phrapview for visualization of data, Repeatmasker for screening repetitive sequences. Vector and *E. coli* DNA sequences were identified by Crossmatch and removed from the DNA sequence assembly process. DNA sequence assembly was on a SUN Enterprise 4000 server running a Solaris 2.51 operating system (Sun Microsystems Inc., Mountain View, CA) using default Phrap parameters. The sequence assemblies were further analyzed using Consed and Phrapview.

Genomic sequence of the KCNQ5 gene and its exon/intron organization

Genomic DNA sequence from PAC 141B1 was compared with GenBank database entries using the BLASTN and BLASTX algorithms of the AceDB package. This comparison originally revealed a total of 5 exons (exons 3(D), 4 (A), 5(B), 6(E), and 7(C) delineated in Figure1), based on their homology to the known potassium channel genes KCNQ1, KCNQ2, KCNQ3, and KCNQ4. Full-length cDNA was rescued from the pools of the human fetal brain cDNA library using the RCCA technique described in Example 2. Comparison of the cDNA sequence and genomic sequence of PAC141B1 revealed a total of 8 exons (exons 3-10 delineated in Figure1). Genomic regions corresponding to exons 1,2, and 11-14 were not present in PAC141B1.

In order to identify the genomic region corresponding to exon 2 and its right flanking intron, oligonucleotide KCN-2L2 (TTTTCTCCTTGTCTTTGGTTGCTTG; SEQ.ID.NO.:11) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2L1 (CCTCAAGTTGCCTCTTGATCCTG; SEQ.ID.NO.:13) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 2 and its left flanking intron, oligonucleotide KCN-2R1 (CAGGATCAAGAGGCAACTTGAGG; SEQ.ID.NO.:15) from the KCNQ5 cDNA in combination with the adaptor primer AP1

(CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2R2 (CCAATTTTGTGTGCTCAGGGATGGTAGA; SEQ.ID.NO.:16) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its right flanking intron, oligonucleotide KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.:17) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-11L2 (GATGATGTATATGATGAAAAAGGATG; SEQ.ID.NO.:18) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 11 and its left flanking intron, oligonucleotide KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.:19) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.:20) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its right flanking intron, oligonucleotide KCN-12L1 (AGA ATT ATG AAA TTT CAT GTT GCA; SEQ.ID.NO.:21) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12L2 (AAA CGG AAG TTT AAG GAA ACA TT; SEQ.ID.NO.:22) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 12 and its left flanking intron, oligonucleotide KCN-12R1 (ACG TGT TTG TTG GCT TTT AAT TC; SEQ.ID.NO.:23) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-12R2 (TAC ACA ACA TGT CCA GAT GAC; SEQ.ID.NO.:24) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its right flanking intron, oligonucleotide KCN-13L1 (TGATCAAATTCTTGGAAAAGGG; SEQ.ID.NO.:25) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13L2 (TCACATCAGATAAGAAGAGCCGA; SEQ.ID.NO.:26) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 13 and its left flanking intron, oligonucleotide KCN-13R1 (GTTTTTCAACCTTGACCACCC; SEQ.ID.NO.:27) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-13R2 (AGCATACTGAGATCGTCTGTGGT; SEQ.ID.NO.:28) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

In order to identify the genomic region corresponding to exon 14 and its left flanking intron, oligonucleotide KCN-2543R(AATTCCAAAAGTGTCTGTCTCTGTC; SEQ.ID.NO.:29) from the KCNQ5 cDNA in combination with the adaptor primer AP1 (CCATCCTAATACGACTCACTATAGGGC; SEQ.ID.NO.:12) was used to PCR-

amplify the DNA from a GenomeWalker kit purchased from Clontech (Palo Alto, CA). Diluted PCR product was subjected to PCR amplification with nested primer KCN-2512R (GGACCCACCTCTTCATCAGTTA; SEQ.ID.NO.:30) in combination with the nested adaptor primer AP2 (ACTCACTATAGGGCTCGAGCGGC; SEQ.ID.NO.:14).

Products obtained from these PCR amplifications were analyzed using ABI 377 sequencers according to standard protocols. Comparison of the full-length KCNQ5 cDNA sequence with the sequences of PAC141B1and sequences obtained in PCR reactions with DNA from the GenomeWalker kit revealed all 14 exons of the KCNQ5 gene. Exact sequence of exon/intron boundaries within the KCNQ5 gene were determined for exons 2-14. The splice signals in all introns conform to published consensus sequences.

EXAMPLE 2

Cloning of KCNQ5 cDNA

The DNA sequence of the cDNA fragment that matches exons 3(D), 4 (A), 5(B), 6(E), and 7(C) of the KCNQ5 was deduced from the genomic sequence of PAC 141B1. Subsequent sequencing of PCR fragments obtained in RCCA reactions confirmed the presence of this fragment in the cDNA library from human fetal brain. This original cDNA fragment corresponds to the cDNA region with coordinates 368-1,004 in Figure 2.

A PCR based technique termed Reduced Complexity cDNA Analysis (RCCA) was used to extend this original cDNA fragment. RCCA is similar to procedures reported by Munroe et al., 1995, Proc. Natl. Acad. Sci. USA 92: 2209-2213 and Wilfinger et al., 1997, BioTechniques 22:481-486 and relies upon a PCR template that is a pool of approximately 20,000 cDNA clones; this reduces the complexity of the template and increases the probability of obtaining longer PCR extensions.

96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 483 bp PCR product using primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32). Eight wells were found to

contain the correct 483 bp fragment by PCR analysis. 5' and 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers , PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primers KCN-DL and KCN-ER because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primers KCN-EL (CTTTCTTTGCACTTCCTGCC; SEQ.ID.NO.37) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2_16_99" that corresponds to the cDNA region with coordinates 278-1,456 in Figure 2. A second round of the RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 2_16_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 117 bp PCR product using primers KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) and KCN-11R1 (CTGATAGCTCGAATGACAGTTTT; SEQ.ID.NO.19) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 2_16_99". A number of wells were found to contain the correct 117 bp fragment by PCR analysis. 3' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-11L1 (GACACAGCCCTTGGCACT; SEQ.ID.NO.17) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer

KCN11-R2 (AAGTGGTGGGGTGAGGTCTTCCACTG; SEQ.ID.NO.20). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 2_26_99" that corresponds to thé cDNA region with coordinates 278-2,527 in Figure 2. A third round of RCCA analysis was performed to obtain the clones extending to the 5' end of the cDNA contig termed "KCN consensus 2_26_99". 96 wells of a human fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 214 bp PCR product using primers KCN-2L2 (TTTTCTCCTTGTCTTTGGTTGCTTG; SEQ.ID.NO.11) and KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) that were derived from the 5' sequence of the cDNA contig termed "KCN consensus 2_26_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers, PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-DR1 (AACACAGAAGGGCTTTCGAG; SEQ.ID.NO.38) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-DR2 (CAGTCTTCCTTGCCATCCTC; SEQ.ID.NO.39). The PCR products were separated from the unincorporated dNTPs and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols.

PCR fragments were assembled into a contig termed "KCN consensus 3_3_99" that corresponds to the cDNA region with coordinates 1-2,527 in Figure 2. A fourth round of RCCA analysis was performed to obtain the clones extending to the 3' end of the cDNA contig termed "KCN consensus 3_3_99". 96 wells of a human

fetal brain plasmid library were scanned, 20,000 clones per well, by amplifying a 145 bp PCR product using primers KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) and KCN-2250R (CATTTTCCTTGGAGGCAACA; SEQ.ID.NO.41) that were derived from the 3' sequence of the cDNA contig termed "KCN consensus 3_3_99". A number of wells were found to contain the correct 214 bp fragment by PCR analysis. 5' RACE was subsequently performed on the positive wells containing the plasmid cDNA library using a vector specific primer and a gene specific primer. The vector specific primers , PBS 543R (GGGGATGTGCTGCAAGGCGA; SEQ.ID.NO.33) and PBS 873F (CCCAGGCTTTACACTTTATGCTTCC; SEQ.ID.NO.34) were both used in combination with gene specific primer KCN-2106L (GCAGCCCCAACAACTTTACA; SEQ.ID.NO.40) because the orientation of the insert was not known. After the initial PCR amplification, a nested PCR reaction was performed using nested vector primers PBS 578R (CCAGGGTTTTCCCAGTCACGAC; SEQ.ID.NO.35) and PBS 838F (TTGTGTGGAATTGTGAGCGGATAAC; SEQ.ID.NO.36) and gene specific primer KCN-2165L (GCCAGAAACTCTGCACCCTA; SEQ.ID.NO.42). The PCR products were separated from the unincorporated dNTP's and primers using Qiagen, QIAquick PCR purification spin columns using standard protocols and resuspended in 30 µl of water. The products were analyzed on ABI 377 sequencers according to standard protocols; PCR fragments were assembled into a contig termed "KCN consensus 3_15_99" that corresponds to the cDNA sequence depicted in Figure 2.

EXAMPLE 3

Analysis of expression of KCNQ5

RT-PCR: RT-PCR experiments were performed on "quick-clone" human cDNA samples available from Clontech, Palo Alto, CA. cDNA samples from heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, and retina were amplified with primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) in the following PCR conditions:

1.	94°C	10 min
2.	94°C	30 sec
3.	72°C	2 min (decrease this temperature by 1.1°C per cycle)
4.	72°C	2 min
5.	Go	to step 2 21 more times
6.	94°C	30 sec
7.	55°C	2 min
8.	72°C	2 min
9.	Go to step 6 19 more times	
10.	72°C	7 min
11.	4°C	

The KCNQ5 gene was found to be predominantly expressed in human retina and brain (Figure 3B).

Northern blot analysis: Northern blots containing poly(A+)-RNA from human heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas were purchased from Clontech, Palo Alto, CA. Primers KCN-DL (GGAAGACTGAGGTTTGCTCG; SEQ.ID.NO.31) and KCN-ER (GGCAGGAAGTGCAAAGAAAG; SEQ.ID.NO.32) were used to amplify a PCR product of 483 bp from a quick-clone human retina cDNA available from Clontech, Palo Alto, CA. This fragment was purified on an agarose gel, the DNA extracted and used as a probe for Northern blot hybridization.

The probe was labeled by random priming with the Amersham Rediprime kit (Arlington Heights, IL) in the presence of 50-100 μCi of 3000 Ci/mmole [alpha ^{32}P]dCTP (Dupont/NEN, Boston, MA). Unincorporated nucleotides were removed with a ProbeQuant G-50 spin column (Pharmacia/Biotech, Piscataway, NJ). The radiolabeled probe at a concentration of greater than 1 x 10^6 cpm/ml in rapid hybridization buffer (Clontech, Palo Alto, CA) was incubated overnight at 65°C. The blots were washed by two 15 min incubations in 2X SSC, 0.1% SDS (prepared from 20X SSC and 20 % SDS stock solutions, Fisher, Pittsburgh, PA) at room temperature, followed by two 15 min incubations in 1X SSC, 0.1% SDS at room temperature, and two 30 min incubations in 0.1X SSC, 0.1% SDS

at 60°C. Autoradiography of the blots was done to visualize the bands that specifically hybridized to the radiolabeled probe.

The probe hybridized to an mRNA transcript that is predominately expressed in brain and retina (Figure 3A).

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. An isolated DNA comprising nucleotides encoding a KCNQ5 protein.

2. The DNA of claim 1 comprising nucleotides encoding a polypeptide having the amino acid sequence SEQ.ID.NO.:3.

3. The DNA of claim 1 comprising a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1, SEQ.ID.NO.:2, and positions 138-2,675 of SEQ.ID.NO.:2.

4. An isolated DNA that hybridizes under stringent conditions to a nucleotide sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

5. An expression vector comprising the DNA of claim 1.

6. A recombinant host cell comprising the DNA of claim 1.

7. An isolated KCNQ5 protein.

8. The KCNQ5 protein of claim 7 having the amino acid sequence SEQ.ID.NO.: 3.

9. The KCNQ5 protein of claim 8 containing a single amino acid substitution.

10. The KCNQ5 protein of claim 8 containing two or more amino acid substitutions where the amino acid substitutions do not occur in a position where the amino acid substituted in KCNQ5 is also present in the corresponding position of any one of KCNQ2, KCNQ3, or KCNQ4.

11. An antibody that binds specifically to a KCNQ5 protein where the KCNQ5 protein has the amino acid sequence SEQ.ID.NO.:3.

12. A method of diagnosing whether a patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration that comprises determining the DNA sequence of a region of the KCNQ5 gene from the patient and comparing that sequence to the sequence from the corresponding region of the KCNQ5 gene from a non-affected person, *i.e.*, a person who does not have Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration, where a difference in sequence between the DNA sequence of the KCNQ5 gene from the patient and the DNA sequence of the KCNQ5 gene from the non-affected person indicates that the patient has Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, or age-related macular degeneration.

13. A method of diagnosing whether a patient carries a mutation in the KCNQ5 gene that comprises:

(a) providing a DNA sample from the patient;

(b) providing a set of PCR primers based upon SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

(c) performing PCR on the DNA sample to produce a PCR fragment from the patient;

(d) determining the nucleotide sequence of the PCR fragment from the patient;

(e) comparing the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2;

where a difference between the nucleotide sequence of the PCR fragment from the patient with the nucleotide sequence of SEQ.ID.NO.:1 or SEQ.ID.NO.:2 indicates that the patient carries a mutation in the KCNQ5 gene.

14. The method of claim 13 where the DNA sample is genomic DNA.

15. The method of claim 13 where the DNA sample is cDNA.

16. A DNA or RNA oligonucleotide probe comprising at least 18 contiguous nucleotides of at least one of a sequence selected from the group consisting of: SEQ.ID.NO.:1 and SEQ.ID.NO.:2.

17. A method for determining whether a substance is an activator or an inhibitor of a KCNQ5 protein or a mutant KCNQ5 protein comprising:

(a) recombinantly expressing KCNQ5 protein or mutant KCNQ5 protein in a host cell;

(b) measuring the biological activity of KCNQ5 protein or mutant KCNQ5 protein in the presence and in the absence of a substance suspected of being an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein;

where a change in the biological activity of the KCNQ5 protein or the mutant KCNQ5 protein in the presence as compared to the absence of the substance indicates that the substance is an activator or an inhibitor of KCNQ5 protein or mutant KCNQ5 protein.

18. A method of identifying inhibitors of KCNQ5 comprising:

(a) expressing KCNQ5 protein in *Xenopus* oocytes;

(b) changing the transmembrane potential of the oocytes in the presence and the absence of a substance suspected of being an inhibitor of KCNQ5;

(c) measuring membrane potassium currents following step (b);

where if the potassium membrane currents measured in step (c) are greater in the absence rather than in the presence of the substance, then the substance is an inhibitor of KCNQ5.

19. A method of identifying activators of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an activator of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is greater than the amount of FRET exhibited by the control cells, the substance is an activator of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

20. A method of identifying inhibitors of KCNQ5 comprising:

(a) providing test cells comprising:

(1) an expression vector that directs the expression of KCNQ5 in the cells;

(2) a first fluorescent dye, where the first dye is bound to one side of the plasma membrane; and

(3) a second fluorescent dye, where the second fluorescent dye is free to shuttle from one face of the plasma membrane to the other face in response to changes in membrane potential;

(b) exposing the test cells to a substance that is suspected of being an inhibitor of KCNQ5;

(c) measuring the amount of fluorescence resonance energy transfer (FRET) in the test cells that have been exposed to the substance;

(d) comparing the amount of FRET exhibited by the test cells that have been exposed to the substance with the amount of FRET exhibited by control cells;

wherein if the amount of FRET exhibited by the test cells is less than the amount of FRET exhibited by the control cells, the substance is an inhibitor of KCNQ5;

where the control cells are either (1) cells that are essentially the same as the test cells except that they do not comprise at least one of the items listed at (a) (1)-(3) but have been exposed to the substance; or (2) test cells that have not been exposed to the substance.

21. A method of treating Stargardt-like macular dystrophy, cone-rod dystrophy, Salla disease, age-related macular degeneration, other forms of macular degeneration, deafness, epilepsy, different forms of neuropsychiatric, heart, gastrointestinal, and muscle disorders by administering to a patient a therapeutically effective amount of a substance that is an activator or an inhibitor of a voltage-gated potassium channel containing the KCNQ5 protein.

FIGURE 1A

KCN6q gene: DNA sequence

1. Underlined nucleotides in capitals represent exons.
2. Initiating ATG codon in exon 1 and terminating TAA codon in exon 14 are shown in bold italics
3. D6D280 genetic marker and phosphoglycerate mutase pseudogene are bold underlined
4. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, 13 and 14 are unknown; these gaps are presented as runs of ten **bold n** as a convenience only

1 CTGGAGTGAG GCGCGGGAAG ATGCCTGGTC CTTGCCTCGC GGACTTGGCA
51 GCCGCGTCCT GCGGGTCTGT CCACTGAACT GCTGAGGACT GCGGCGGTGG
101 CCTGAGGGAG AGCCGCCGGG GCAAGCAGGG GGCCCGG***ATG*** AGCCTGCTGG Exon 1
151 GGAAGCCGCT CTCTTACACG AGTAGCCAGA GCTGCCGGCG CAACGTCAAG
201 TACCGGCGGG TGCAGAACTA CCTGTACAAC GTGCTGGAGA GACCCCGCGG
251 CTGGGCGTTC ATCTACCACG CTTTCGT**nnn nnnnnnn**ttc cttttctatt
301 cttattatta atatatgatc ttattattaa taatataaag gaatagcaaa
351 tgagaatcca tgagcaatat cagaccatga aaatgagcca gtggctgagt
401 aacaaccaat taggacactt gatagtttag caaagttgcc aaacaggaga
451 cagactcggc tcctttgaac gaagagtgac tgcagtgtgg attccccaga
501 taggagagca agaacatact ttctgggcct ctctcaggat cgttgtttgg
551 gaaggaagtt gtatgggaaa ttcacaaact cttagatgct aacatttaaa
601 tgcagcatgc cacacacaca aacccacaaa cacaaccttt ttttcatcaa
651 taaaattgca gaggagcccc atttgcacag tatatcacat tgtattttaa
701 tatccaaaat ggctagtccc ttccagagtt tttatgagtt aatgtgtgct
751 aatttaatgg gcctggtgct ttattcattt gaagcaagaa attaagtctg
801 tgataataag gtaaggttct tatcagattt ctctttttgt tgttttacag
851 TTTTCTCCTT GTCTTTGGTT GCTTGATTTT GTCAGTGTTT TCTACCATCC
901 CTGAGCACAC AAAATTGGCC TCAAGTTGCC TCTTGATCCT Ggtaagtgaa Exon 2
951 acatgaacaa gaacgtacat gaatgttgta taagaactgc ctataacatt
1001 tatactatgc atcttatcct acaaaaaaat cctatctaaa aaagagttac
1051 tgagaaatat aaaaatgtca aagattactg aaacatttgc ccaccaattt
1101 aacatgtagt caatccttag aaatatatag aaatgttcag gattgctatt
1151 acacagcaat atcttgtgtt gtagatatat cataaataga aggcaatatt
1201 agaaagcagt tttaagtatg tttatctatg ctaataaaca aattatataa
1251 gaagaatcag tatctatgag gcctctcatt atattgtgaa agactataga
1301 gtagagagca ttttccaata actgtaattt ggcagtagct aaatataatt
1351 ggccaagaac tatgaacata tggcacctca taagaaaata gaaggctcct
1401 tcatgctctt ttcaaccaac agactgcatt atgagttttg ctgctaatgc
1451 agttacctgg tgataaattc tgcagtttgc tctgtttcca ttatgctgtc
1501 aatcctcaac cacacagaat tgctcaattc actttt**nnnnn nnnnn**acgag
1551 gtcaggaggt cgagaccatc ctgcctaaca cggtgaaacc ccgcctctac
1601 taaaaataca aaaaattagc tgggcgtagc tactcaggag gctgaggcag
1651 gagaatggcg tgaacctggg aggcggagct tgcagtgagc cgagattgcg
1701 tcactgcact ccagcgacag agccagactc cgtctcaaaa aaaaaaaaaa
1751 aaaaaaaaaa gagtatactt gatttatggc atgagtggtc ttgaatgatt
1801 ttgatggatg actggaaaca attagagata taaataaata gcacagaatc
1851 atgacagatt tcatgaagaa tacactgtga agattcacat ggttaataac
1901 attgaaatta ttaaaataaa agagactgca tatattagat ttttctttgt
1951 gatctagttg ttcaaagcag cagaaaactt taaattttcc ttaattttga
2001 aagtgtgatt aatggaatat tgttacaatg ccattgattt atatactttg
2051 aggatagtta acttctttat gtttattaga aattgcactg agagctaata
2101 tgcagtttct attggtggtg atatgttctg ttaacagggc ctcctgtcag
2151 tttttattct gagatttctg cctttcctgt tcttttgcat gagcctaact
2201 gactgagttt caatatcaag ttctgaaagc aagtgagcat actagtgtgc
2251 atgcaatgtg cacagaaaga tgtgttttcc tacctctcaa agctcaccaa
2301 aggatattac tcatattgcc acaaagtaca tttacaccaa taacacatac
2351 tttggtaatg ggaaaaataa ataatcttag gtaataaaat gcactttggt
2401 gcttataaag gaaaataatc atcacaggta gaagaggagg aaggcaagac

FIGURE 1B

```
2451  taggttttga ttcaaaatgt tttctgtttt gctaggaagt ctagaaggaa
2501  tttggtcaaa tgacctgagg aggcaaggag atttctccca gtggcacatg
2551  gcagtccaca agaagactag gggcagggaa acaaagcaag attgtatctg
2601  atttctacag gactccaaca ctaccctgcc aataccottt tctcctctga
2651  aagccatgat cccaaaggtt tccatttctt ccgggttttt cacattctac
2701  caacaagcag aatgtcttcc ccactgacag ctcaacagtt gagtttttcg
2751  gggttctacc ccttcatcaa cacagccttt gctttcctgg ttactgagta
2801  aataaaacac actggccact tctgcttagc cttcaggagc cactctggct
2851  ccaccctgaa gttccatttc ctccaagaac taagacattt ggagattctg
2901  cctaaaatat gcttaaataa aagggataaa ctgtctctca ctttctttcc
2951  cccacagctt gtcttaagaa caacggtgta accattagtg aaaaatcctt
3001  tcaggctagt aaaatgtaaa aagagaagag gtatcgggta acaacaaatg
3051  aaaataaaat cattcagtgg tagaaaccat aggagtgaaa ttaggtagtt
3101  actgtcctcc agcttacatt aatcaaaata agcccacact gtcactaaga
3151  catcttgcag taagaagcca ttcaccctct cattgcaatt agtgtcataa
3201  agctgaatag acaggtcaga aatgaaaatc ataggccaat taagttattc
3251  tcatttttcc acctccagct agctcttttt gagaatttg atttaatag
3301  ataataaaac agtatgctaa ttgggtggtg ctgagcctga agccgtgaac
3351  tgaaggaaac ttcaacaaac atttggctag ggcctgctct aagcagaggg
3401  gctacgacaa tgggtaaggc atttctctag aaaccagcac tcagcagaat
3451  ttctggcacg agattttgtg agttttctag tggtgtgtct tatcttcccc
3501  caatagatta taaactcctc gagggtgaca gaacacattg ctgatcttta
3551  tatcctgcat gtttatggta ttcggtagac atttataaaa tgaattcatg
3601  aaaagcagaa catctagaaa tgaagtcaac attgcagaga agttagctat
3651  atgaaactct gtaaataccc tcaaggaaga aggaagaagc agattttctg
3701  gaaatcaagg gacctcccag tataagagca attcctttgg tccaaagaag
3751  ggcagctata agaacagaga cataactcct ccgtaagaaa agataaaaat
3801  tctgaaagtt ctctaagaac atgcccagcc ctgacctgcc tctcactctc
3851  agtagcatgg aagccgtact atctcttatc ttgacacaag catccacttc
3901  aatccacagg acaaatatca ccaatatgag aagataagat ctgttttata
3951  gtcaacttgg ctgacatgta ctaatttctc aaggtcagga tagctctcta
4001  aatagaaata cttgtttgtt ttaaggaatt ttatttaaat ttgtgtatct
4051  taaattttaa ttttgatctc ggctcactgc aacctccacc tcccaggttc
4101  aagcaattct cctgcctcag cctcctgagt agctgggatt acaggcacct
4151  gtcaccatgc ctggccaatt tttgtatttt tagtagagac cggatttcac
4201  catgttaacc aggctggtct caaactcctg acctcaagtg atctgcttac
4251  caaggtctcc cagagtgctg agattacggg catgaaccac tgctcccagc
4301  ctcatgtagt tcttaagagg aagaaaagcc tatagattag tgagaagtag
4351  acaaattagc aatttgaatc aaatgaaaac ttggtttgat ttcattcatt
4401  ttggagacac tttcggtgtt tccattttga tctgattcag gacactgatc
4451  ttcgattcta agttgcactg gttaatttgt gattatttta caaaatcata
4501  acagaataca tatctgggtc cagttcaagg tacagcaagc cattttcaat
4551  gtttccagct tggtgtttat gattcataca tgaatcattt gggcatgcag
4601  acacacccaa atagaaacct caaaccaatt aaggtataaa taggtttagg
4651  atgggggagg atggacaaca aaaaaaacct cagtaaggct cctccacaaa
4701  gggcaccact tcagcttggt cccatgggca gacttcacct gtggcaggtg
4751  aaggggaaag cctaagacat cctgtgccct gatgcagatg tgacttacag
4801  aacataaaac gtaaaggcag aagggatcat ctgggtggct gctcatacta
4851  ggcaggcatt atagctgctg acaagagcca acccatccct aaggatctaa
4901  aatcactaca agagaggacg gaagtcctct catcatggca tcccaactag
4951  taactgggat gcatagggcc actccaggta ggcagcgagg ggtaaaccag
5001  gaatgtcctg ctgttcccac ctcttttccc caagcagggg gcacccactt
5051  cctgcctcca gcccatatgg tctcaattta tggcctcaat acctgataaa
5101  aaaccagccg tgatccttcc ttagtaacaa agtgtcaatc agtcatttgg
5151  aatggggcat tttcaaacta ttgcctccct atgatcttct gaagaacctc
5201  tgggataaat gaacattgtt atttaggtat ggttaaatga attacttttc
5251  aggagcagat ttatatatta acaggtgtga aaaacttgaa tggataaatc
5301  atttataaag aaatttcagg aatcaactaa tcccaagggg aaagacccac
5351  taagacacta gattttgctg gagctactca aacaaattca tctatcatat
5401  ctacctaagc cttccaatca atgagactag ccgcagtgac actgtctgtc
5451  aaaactacct cagtcatttt tttccaaggc aggaagcatc catacccctt
5501  cacaccttaa tctaatttcc cctatctcca ccccactccc acttctatga
5551  ccccccttccc cccataccca cccccgaagc atctactagc caacttagtg
```

FIGURE 1C

5601 aagttctgtc acgctctcac aaccacctct gtgcagcaat gattctgtaa
5651 atatccatgt gtcctcaaca ccaggtcaaa ttagtccctt tggtaaaaac
5701 attcattccc tcaaattctc ttccaataca ctaatatacc ttcccaaaaa
5751 gtaaggagaa gcttgaaagc tagctggatt gatgatggta tgtgatgttc
5801 tataagttat agttagtaag catgttttta ggatattttt ctgctctcca
5851 aagagacaca attccggaag atatttactt ttgtgtattt ccacattttg
5901 gtttaagttt ggagccatct ctagatctta atttcattcc cctaatatgt
5951 gttatactag tagaatttc caaattacat agaattataa ctgcaactct
6001 tctgactgat gccttttttt tgcattttat gatgcagttt acatcacaaa
6051 ttctttccct gcagggatta tgtaaagagg catgttgacc tgctagccct
6101 atgttacttt aagtatatgc acacacacaa aaaggaacaa aaacagctgg
6151 gaattgatta tgttgatatt ctgaataaaa gcaatagttc taattatgta
6201 tgtctaatta gccacagctc ttcaagaatt gctgcaaatg tcacagggtt
6251 tataatgtcg gcatttcatc ttcacgaaaa tgctatttga tggcataaaa
6301 ccagaaaaaa ctaatggtca cagaagacag cttgtagatt agacaaaggt
6351 cactgtgttt taatgaacag tgctgttaat taatgagaaa acaactggta
6401 catgagcttt taagcattgt gaatttgtac ccaaaaaatc aatctgccta
6451 aaacaatttt aagtagctaa aaaacaaaat aacggcaaga acataattta
6501 aacctcaaat ggtacagcag agttatatgt atcaattaaa ttgaatcaca
6551 gttctcaggt gtgacatatg aagaggcttc tttaatgcct ggaaaagagg
6601 gttaatatgg attggtattc tcaatacata ttgtagataa aattcaagac
6651 tagctctacc actgcctctt ttcttttttt ttttttttt ttatttgaga
6701 cagtatctcg ctctgttgcc caagctggag tgcagtggca tgatctcggc
6751 tcactgcaag ctccgcctcc cgggttcacg ccattctcct gcctcagcct
6801 cctgagtagc tgggactaca ggcgcccgcc accacaccca gctaattttt
6851 tgtattttta gtagagacgg ggtttcacct tattagccag gatggtctcg
6901 atctcctgac ctcgtgaccc acccgcctcg gcttccgaaa gcgctgggat
6951 tacaggtgtg aaccaccgcg cccggccacc actgcctctt aggcttctta
7001 atttccttat catttaagaa gaataagaaa atgcttctat gttttaccaa
7051 aattctgtga ggacaaatga ggaaccattg taactcctac aaggtgagtg
7101 ataaaaataa tacacattta ttgtctttgc ttttgtaaag agttatccaa
7151 gccaagcttc taggggctta aataaggaag gacaggacca ttgttaataa
7201 catcaagttt ccactacagc tttcctccaa acaagtcaaa tattctgaat
7251 attattcact aatctcttta gctgccattt cagtaaatag cgagcatttt
7301 atttcaacta aaaccaagca agagaaaatg aactgcttta tcctgaggta
7351 cagcagcaaa ggcaccagaa cttgtctcat ggcttaccca gcaagggtca
7401 gaagaaccat ccctaattta aatcatctcg actgaatgta acagattttt
7451 gtattttcaa ctcatatgaa aataaaacaa tgagacctca tccaaagggt
7501 gatttagaga gtacctctaa acaaaacaca gtgaaaatag acccagcatc
7551 tggatttgaa gaacacattt cctcttacga gtctatccca ttgtctagat
7601 tgctggcaat ggctttttta aatttaaatt gttattgaga taattgtaga
7651 ttcacatgca gttgtaagat atagtagaca taccctgtgt atactttacc
7701 caatttccgc aaaaggtaac attttgtaaa actatagtat aatatcacaa
7751 ccaggataat aatattgata cagctcacaa a**tctcattca gatttctcca**
7801 gttttacttg aatacatttg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg
7851 tgtgtattgg ctctgtacag ttttatcact tgcagagatt agtatatcta D6S280
7901 aaacaacaat caagatattg gacagttccg gccgggcacg gtggctcact
7951 cctgtaatcc cagcactttg ggaggccgag gcaggcagat cacgaggtca
8001 ggagatcaag accatcctgg ctaacacggt gaaaccacgt ctctactaaa
8051 aatgcaaaaa attagctggg cgtggtggtg ggcgcctgta gtcccagcta
8101 ctcgggaggc tgaggcaggc gaatggcatt aaccagggag gtggagcttg
8151 cagtgagccg agatcgcacc actgcactcc attctgggca acagcgcgag
8201 actctgtctc aaaaaaaaaa aaaaaaaaaa gatatcggac agttccattg
8251 tcacaaggat ctctcaagtt accccttgct aaccacatcc accttctcct
8301 tcacacttgc acaccccttc ccttctccag cctgacccca gcagccacta
8351 atctgttctc catttctgaa atgtttttat ttcaaaaatg ttatataaat
8401 ggaataatac agtgtataac tttttaagac tgacttttct tgcactcaat
8451 ataattccct ggcaattcat ttatgttact ctgtgtatca atagttcatt
8501 catttttatt attgagtagc attccatggt atggaggcac cagagcttgt
8551 ttaaccatcc tcatggtgaa ggacatctgg gctgttttg gggtctggtc
8601 attatgaata cttcttctgt gaacattcat gtacaggttt ttgtacaaac
8651 ataagttttc atgtctctga cacgaatgcc caagagtaca attgctgagt
8701 catatggtaa ctatatgtcc agttttataa gaaacgacca tgctcagaag

FIGURE 1D

```
8751  gaccatactg ttttacattc ccatcagcag tgtttgaatg atccagcttc
8801  tccgcatcct ccccagcatt ttgtgttgtc actatttttt gccactattt
8851  tttattttag ccattctgct agctgtgtag tgataccatt gcgatctaat
8901  ttgcattttt ctgatggcta atgatgtcaa ataacttttc atgtgcttct
8951  ttgccatatg tgtaacttct tttatgtatg tcctctttta tgaatatcct
9001  atttatacct ttgccaattt tctaattgag tttttggttt tttactgttg
9051  agttttaagg tttctttaca tattttagat attagtcctt tgtcagatat
9101  gtggtttaca aacattttct cccagtctat ggcttgtctt ttcatcctta
9151  gtacctgggc tctcacagag taagttttta cttttgatgg agtccaattt
9201  ctcatttttt ccttttataa cttctgcttt tgatgtcaag attaagaact
9251  ctttgcttag tccaaatccc aaaaatatct ccattttttt cctaaaagtt
9301  ttattatttt atgtttaatt tttaaacccg tggtccattt ttaaatgatt
9351  atcataagat aggaagtata gattaaggtc cacttttttg cctatagatg
9401  tccaattttt ccagcatcat ttgttgaggg cccttcttcc tccattgaaa
9451  tgcttttgca cctttaaaac aaatcaattg agcatatttg tgtgggtcta
9501  gttctgaatt ctctattctg ttcactgttc tatatgtctg tatgttccat
9551  atgtctatcc ctccaccaat ccacagtctt gattactgga gctataatag
9601  taggctttaa tatcaggtaa agtgattgat ctcgttttat tcttctttgt
9651  cagcattgtt ttagctattc caggtcctgt gcatttccat ataaatttta
9701  aaataagttt gtatctaccc cccaaaaaaa actttgctga gattttgaca
9751  ggaattttat tagacctgta gatcaatttg ggaagaattg acatctttgc
9801  tatgatcagt cttccaattc ataaacacgg tatttctcct cacttattta
9851  ggtcttttct gatttctttt atctgcattt cataatctca atgcacataa
9901  accgtatgtg tttttctaag tggatattta agttattttt atttggaatt
9951  attataaata ataattttgt gtttctaatt ttcatttcca catgatcatt
10001 gttagtataa agaaatatga ttaattttta tattgatcat acatcgtgca
10051 gccttagtga actcacttgt ttcaagagtg tcttcgtaga tttcttggga
10101 tttttctgta gaccatcatg ccatttgtaa atagagacca ttttatgttt
10151 acctttccaa actgcatggt ttttttttctt ttatttggct tattgcagca
10201 actattaata taacttacaa tactatgttg aataagagtg atgaaagtat
10251 acatcttggt tgttcttaat gttggggaaa agcattcagt ctttcactat
10301 taagtatgat gttaagtttg ttgtaaatgc tatttatcga attaaactgt
10351 taaacctctt ttcctaactt gccaagagtt tttttaatc ataaatgggt
10401 gttggatttt gtcaaatgct atttcgtcat caatttatgt gatttttttt
10451 tagctttatt atataatgca ttatattgat tgatttcaac cattgagcta
10501 gccttgcata cctggaataa atcctacttg cctatatatt gactgattga
10551 ctgtttgcta atattttgct gaggattttt tgtgtctaag tttatgataa
10601 atatgggtat gtagtttttg ttttgctttg ttttattgtc tttgtctggt
10651 tttggtgtca ggataatact gacttcataa aatcattgag aaagtttttt
10701 ctcctctatt ttctgggaga aattgtgtga aaatgatata ttcttattta
10751 aatgtctggt tgattttgcc agtgaaacca tttgacctgg acatttctgt
10801 ttggggagat tttaaactat gagttcaatt gctttagcgg ttatagggct
10851 acctagattg tctatttctt ctttgttgag ttttggtagc ttgtagtttt
10901 aaaggatttg gtccatttct tctaagttat caagtgtatg tgcgtaaagt
10951 taccatagta ctccttcatt ttttcagtgg cgtagaatct atactgatat
11001 cccctattac attcctgaca ttggggattt tcatcagctt tcaagaaaga
11051 gatttatcaa ctttattgat tttctcaagg aaccactttt ttgtttcatg
11101 gattttccat attgttttcc tcttttcagt ttcattaatt tttgctcttt
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11251 ttcatctaca atgtaagcat ttagtgctat aaatttcct ctcagcactg
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11351 agttcaattt ttttaaaatt tttgagactt tctctttgac caatggacta
11401 ctgggaatat tgtttaattt ccacatgttt agagatttgc ttgttgtctt
11451 tctgttattg atttctagtt ttattccatt gtggcttgag aacacattct
11501 gtctgatttt attcttttaa acttgttgaa atttgtttat gacccggaat
11551 ataatctatc ttaataaatg tgcatgggtg ctttttaaaa atgtgtattc
11601 tgctgatgtt gggtgaaatg tctcatatca gtcagatcct gcaggttgaa
11651 tgtgttgttc aaatagttca catacttgtt aattttcatt ctagtagtgc
11701 tatgcccata gttctgagca aggataaggt gggttgatga agttcccaaa
11751 tacgacttaa catttgtcta tttttccttt cagccctatt ggttttgctt
11801 tatgaatttt gagactgtct tgtcattttc ccctcacctt cttaaaaaaa
11851 aaagcagcaa gcaatatttc tgaacaatag ggcttgaata aagaacttgt
```

FIGURE 1E

11901 aaatgtactt tatcctgcct tactgcagca gaggaatagt gcagtgacct
11951 tggcatacct aagaacaatg ggcatatatc tgtcatttgt taagaacaat
12001 ggacatattg gtgtcatctg tttccatgaa aaagaaaaat tactacacag
12051 tagtgttcgg gggctcaggc cacatttggg attttcttgg gatccccttat
12101 aatatgagta ctcacaactg gagtgccaaa tgtcctggca taagcaggaa
12151 ttaggggcag ggattaaaaa gtggatctgc cattcaacct aggttgggca
12201 caggcacaac tacatgggca ttttgggcct gagtatgttt tccatatttg
12251 gaaagatgtg ctggattaac aagaaatgat ctggcacttt agatacctta
12301 ataaatgaac agactcaact acccagatat acattcaaaa ccaaaacaaa
12351 gccaaaatca aacaaaacct tcggattatt aatgaatgta tgttgaccct
12401 aattttggtt atctgtgcat aaagtcatct ttgaaggttt atcctataag
12451 taattttgaa taactgtgag taagcagtga tgatattggg tatttatttc
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12551 agaatgatat agctctacta ggcatttcaa aagtgcagca tatcatcaca
12601 tgctctaatt aaagaaacag acatttgcct gaaatttgca acaaaaatgc
12651 cacttttata aatttggtaa cagtttttat cctgcgagta agaatgggag
12701 aatggggagt aggttagaat gtttactttc tctgctttgt atttctgtga
12751 tgtttggaag ttttaataaa gacaatatat tacttttaca attaagctat
12801 tataacaaca atctataaat attgttctac attataaatc ttgaatcaac
12851 cctcgtttta aaacaagaaa gtgaattatt ttttaaagga aaaacaattt
12901 tgataaataa agtgcctgtc cctatagaga cagcaaggtg actgtgctaa
12951 gcttgctcca gaaatgcttt cgttttacaa attccatttg gtttttcatt
13001 ctatcatcga ctgtttaatg agccactcta gctggccttt ccccagggtt
13051 aactcacaac tcttcctaaa taatctcagt cattttcctg gagcaggtgt
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13151 cagatctgga ggattcaggg tctcatttct ggcaaaggat atgtgtgtca
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14251 taggggaaca ttgatttcag tgagtataaa aaaccctttt tgctctacaa
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14451 tctgaaatat gaatccccca ccctccaatc caaaataccc aaatacatag
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14551 cctgggttct agcttgaaat tgtacttcct aatgaagatg ccatagagca
14601 ttctggaatt aagatctagc atttcccagt aatatttaaa agtattataa
14651 aatggaaaag tctatatata aaagctatta ttattattat ttagtagcta
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14751 aaatccaaat actgaaaatt cttgatgagg cttatttatt tcaactattt
14801 tcaacctgaa aaagtaggtt tttaatttac aaaatagttt aggctatctt
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14901 cgtaatcttc tcagtttcct cccttactcc tgttccctat ggtgggggca
14951 gagtggattt aaggaagaaa gtgtatcacc atccatgggc actgttaaga
15001 agaatccttt attccatact tctttcatag tatgcacatc tcaaaagtct

Exon 3(D)

FIGURE 1F

15051 ccacttatta aaccagaatt tatggaaatg tggctgtgtg tgaggcactg
15101 gtgttacaat agtgaatcta gtggaattct cagttaaatc tatcttaaaa
15151 taccttgttt ggccctcacg aatgcagtct gtttgtctgt cttctccaat
15201 aataggcttt actgcttttt ggaagccatc atgctaaggt atggagcaaa
15251 gtcggtggta actccaagcc ttgcaggttc ataaagcccc aaggcatatt
15301 agtgaaggca ttagattttt ctccctggag atgctttttt ctctctgaat
15351 tctctactca ggcagcatta caaaggactg taacctgatg tgaaactact
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15451 aaggcagatg gttagccaag attcactcaa cttctacagg ataaggtcag
15501 ttcatggatg actggaaaaa tgtttcattc cagattttaa aaccaattaa
15551 aaattggttt tgttccaatt tcagaagcaa tgccaatgta tctctggcct
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15651 tgttttcagc tacggataca tcaacacatc ttagtccttt agtctttctc
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18151 tattacttct aagtgttcaa actccctcag tgcatgtaga ttccttccat

FIGURE 1G

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21201 gcttataaag cagcaccatg tccctctgag acattgttta cttcactcta
21251 tagatggaaa agtcgaggca ctgtgaagtg ggggtgcttt gtccttagcc
21301 cataaatcag cagtaaagct aggaatagca tgctggcctc ccaatagctc

FIGURE 1H

21351 attgctctaa agcactgcct cttgttagag tcaaatttaa ttatagtata
21401 atccgtttaa tctacatgtg gagaaataat gaaggagcag gaaaaatgaa
21451 tttcttaaca gatcagtgga aaaccatatt acatagatta gcaactgtct
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23901 ccagaataca atcacaaata taacggcaga atcgatcaag ctgaggaaag
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24001 ataaagaaaa aaagattaaa gaagaatgaa caaaatctcc aaagtatggg
24051 attatgtaaa gacaccaaat ctatgactca ctgatgtccc tgaaagagag
24101 ggagagaaag caagcaactt ggagaacata tttcaggata tcatccatga
24151 aaattccccc aacttcacta gagaggccaa cattcaaatt gagaaaatgc
24201 agagaaccct tgtgagatac tatacagata accatcccca agacacatac
24251 ttgtcagatt ctctaaggtc aaaacaaaac aaaaaatgtt aacagcagct
24301 aaagagaagg ggcaggccac ctcccaagga aaccccatca ggctaacagc
24351 acacctttca gcagaaactc tataagccag cagagattga ggacctatat
24401 tcagcattat taaagaaaag aaattccaaa caagaatttc atatccagcc
24451 aaactaagct tcataaatga aggagaaata agattctttt caggcgagca

FIGURE 1I

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24551 agagagtgtt aaatatggaa aggaaagatt attactggca actacaaaaa
24601 cgtgcttaag tacacacacc attgatgcca aaaagcaacc acacaaacag
24651 atctgcataa taaccaatta acaacacaaa acaggatttg atccttcaaa
24701 tccacacata tcaatattaa ccttaaatgt aaatgggcta aatgcccaat
24751 taaaaggcac agagtggcaa gttggacaaa gaagcaagac ccaacagtat
24801 gctgtcttga atagacccat ttcacatgca gtgacgcaca taggatcaaa
24851 ctaaagggat ggagaaaaat ctaccaagca aatggaaaac agaaaaaagc
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27501 tctctctgaa gaggctatca tggagctgaa cctgccaact ggcattctca
27551 ttgtctatga attggacaag aacttgaagc ccatcaagcc cagcccacgc
27601 agttcctagg ggatgaagag accatgtgca aagccatgga agttgtggct

Phosphoglycerate mutase, processed pseudogene

FIGURE 1J

27651 gcccagggca aagccaagaa gtgaaggcca gcaaacaggc accctccctg
27701 cccattgcat ccatctgtcc ctccctcctg aacatgtcac actgaccaca
27751 tctatagaca tcttgagttg cagctgcaga tggggaccgg tggctcccat
27801 tttcatttta gccattttgt cttctgcacc cactcccttc atacattcta
27851 gtcagaatag cacttctagg gcacaggttc tcagtctaag ctgtggaaaa
27901 gcccccgtta tccaagagag ttcaaagata gtgacttggg tttttgcaag
27951 tgctttgttt actaaggact tgtgaggagg agccatgctg agctacgacc
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28051 ttgtctgtag tcaggccact gcctgggggc tctagtcatc ccagtggaag
28101 atgaatgtaa cctgcatggt gatgtgacag ctgtttcctc cctgacccca
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28351 ctccttgacc tttgaggggc aggagtgctt catgctgtgt gttttagaat
28401 ccctccctgc cttgtttcat ggcagtgaaa tgcctcttgg tcctctccaa
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29351 cagctaacca ggtaggtgaa agatctctac aacaagcatt ataaaacact
29401 gctcaaagta atctgagatg atataaacaa aaggaaaagc attccatgct
29451 catggatagg aagaagcaat attgttaaaa tggccatatt gcccaaagca
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30651 gagaaatgca aatcaaaacc acaataagat accatctcac aaaagtcaga
30701 atggctatta ctaaaaagtc aaaaaataac agatgctggc aaggttatgg
30751 agaaaaagga atgcttatat actgctggtg ggaatgtaaa ttagttcagc
30801 cggtgtggaa agccgtttgg caatttctca aagaactcaa aatggaatta

FIGURE 1K

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30851  ccatttgacc cagtaatctc actattgggt ttattctcaa aggaatgtaa
30901  ctcattctac cttaaagaca tatgcactca tatattcatc acagtactat
30951  tcacaatagc aaagacatga aatcaaccta catgcccatt gatggtggat
31001  tggataaaga aaatgtggta catatacacc ataaatacta cacagccata
31051  aaaaagaaca agatcatgtc ttttgcaaca acatggatga ggctggaggc
31101  cattcaccta agcgaactga cacaggaaca gaaaaccaaa tacacatgtt
31151  ctcacttaca agtgagagct aagcattgag ttatatggtc acaaacaaga
31201  gaacaacaga cgcgtaagcc tacttgagga tggaaagtgg gaggagggag
31251  agcataaaaa aactacctat caggtactat gctttttacc tgcgtgatga
31301  aataatctga acatcaaacc cccataatat acaattcacc tatataacaa
31351  acctgcacat gtaccacaga acctgaaata aaagtttaaa aataaatcat
31401  aaaataaaat gttgaaatgc ctagaatgtt tcatagcatt aaattagacc
31451  atgctgtctt aaatgacatc ttattttcat agaaatcatg tttctgcttt
31501  ttctgttttt ctatgaaaat ttttttaaca agcagaagtt aacgaaatgt
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32201  atctatctta ccagattcca agataaactc caaataaatc aaagatttaa
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37101 gcttagacca aaaaccctga agtcagcctt agactccctc gtttgtctca

FIGURE 1M

37151 tcccacagtc agtccttcag caagtcttgg cctctccacc ttcacaatgt
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FIGURE 10

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FIGURE 1P

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49101  cgtgctaact gtggctattt cgacctgttt ctttcagATA CCATTGTTCT
49151  TATCGCTTCA ATAGCAGTTG TTTCTGCAAA AACTCAGGGT AATATTTTTG   Exon 4(A)
49201  CCACGTCTGC ACTCAGAAGT CTCCGTTTCC TACAGATCCT CCGCATGGTG
49251  CGCATGGACC GAAGGGGAGG CACTTGGAAA TTACTGGGTT CAGTGGTTTA
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49551  aaaatctttc attcctttta tatctagGAA TTAATCACAG CTTGGTACAT
49601  AGGATTTTTG GTTCTTATTT TTTCGTCTTT CCTTGTCTAT CTGGTGGAAA   Exon 5(B)
49651  AGGATGCCAA TAAAGAGTTT TCTACATATG CAGATGCTCT CTGGTGGGGC
49701  ACAgtaagta taaaaataca tttttattt attggatgtt gtgaattgtt
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FIGURE 1R

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FIGURE 1T

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59651 tagaatttgt ctccctcttt atcaaacctg cttctgaatt gttccccctc
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FIGURE 1U

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FIGURE 1W

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77551 tggtttataa tgtgtgctac ttaagagaca gatgtgcaca atggagtatt
77601 tttctcttca gatccatttg agtgaaaagc atatgacctt aaagggtgtt
77651 aaacatgtca gatgatttat tcattgtgtc atcatcattg attttttaa
77701 tgagcagttt ctgtatctta tcagaataaa gggcacattt atctgccccc
77751 aagcttctga ttattttctc cttagtgaat gaagcctgcc tttctcatgc
77801 ttttattctc ttgtgtcttt aaaggcagct gttcaaaata ttacagtttg
77851 cccccatttc caagttcttg cttttgttcg ctccacctgg ggtagggaag
77901 gaggagccaa taaaaaggag ggttaacgcg gtgggagcag aagtgcttaa
77951 ggaaaataga tccagtcttg ctccagacac agctcaagct gtgccaacca
78001 gagaccccag agcacctctc caaagctctt ttaggtggta gggcttctcc
78051 tctgcctatt aataagtgca gagaacaccc ttgtcccacc agtgcccaac

Exon 6(E)

78101 ttgagattca ccagatcgtt ctgccccaga acactcaaaa tcacagaaaa
78151 gagactgaaa aggccatgca tatgcttggg tactagacct cagtttgaat
78201 acatctttgt cacatactaa ctatatgact gctttagttt actagggctg
78251 ccttaacaag taccacagac tgggtgactt aaacaataga aaggtattgt
78301 ctcacagttc ccaagactgg acgtccaaaa tcaaagcatt gagaaaccac
78351 gagagccatg agagaaagaa ctgttccagg cctctcttct tggcttatag
78401 atggctcttc ttcctgtgtc ttcacatcat ctgtgtccaa atttctactt
78451 cctagaagaa caccagtcat atttgattag ggtccatcct aatgacctcg
78501 ttttaacttg attacctctg taaggaccct attttcaaac aaggtcacat
78551 tctgaggtca tggggattag gacttcaaca tatgaatttt ggaaggacgc
78601 aattcagcct gaacagtgac cctgaataag tttctttttt aatagaatgg
78651 aggaagaatt attgagccca gagaaatttt gtgcggacca atgtaataat
78701 gtaagtcaag tgcttgtcat gaagagaact ctcaataaat gttacttccc
78751 tttgcctgta tgaatctaga aatacatgtt tcctggaaca aaacgatgaa
78801 atccaggaga attaaaaaaa aaaatcttac gtatccaagg caacttcatc
78851 tggcaatctc aacaattcag aacagagaag agattcactc aataatcaga
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79201 aagattataa acaataaata tagaggaaga tgatagaaca aacactgcaa
79251 cagaaagaaa tggtaaaaga ctaacagcaa agaagggaaa aggaaatctg
79301 tgagtagcaa gcagacatca atgttcaaaa tgtgtatcct gtcagtaaaa
79351 ataaaattaa attaaaaggg aaaacaaaat gtatgaagat ctagggccaa
79401 ttagtgttag ggtcaacaaa cctctggaag ttggctgcac ccagcacagc
79451 aaaaaggcag tccccataat gaaactctaa actatcacag ggaggttaaa
79501 tatgtcacta ggttaagtta aaggtcagag actaagtagt cattcttgga
79551 aatgtttcca ataaagtaag tatgaaattt ttatatgcaa attaaattaa
79601 cctatgttgg aaatctgaaa attttgcttt cacagaaaat tacatttctt
79651 aagaacccca agaaaagtaa cctctactaa ggatctttta ctgaaacttc
79701 acaatatttt ctgagtcctt atttattaaa tgaaagactg aatggtccat
79751 atataccttt agaaaaaaac aagattgcca gagattttat tatatcctgt
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79851 gacattttgc tgagaaagct agaggtggat tgtgggctgc ccctatgtag
79901 ggttcctccc acccaggaca cctgagaacc aagaaagaaa agagcctttc
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80901 ccaagctgtg tactaagaga gaggtggaaa aaaattggaa aggagccatg
80951 atgagacaat aagcagacct ggtttaataa ctgctgtaat gtacagtctg
81001 gcgcaagaaa tacgtagtga acatttacca ttcactaata tatgttaccg
81051 agcaatgcca atgtgatttt cagcacattt tagattgttt ggcagatgat
81101 aaatttgtgc tatgtagggc ctgtctttat tttccaaagg ggattaaact
81151 ccgaacctca catccacatc ataagtgctc aaaatggtag ctagtgctgt
81201 taattcaatg tctgcaaaat ctaaattatg ctccatacaa gtggattata

FIGURE 1AA

81251 cacatatatg cacataaatg catgtatata tactacatat tataaatata
81301 tgccagaaat tttggtattt catattctct tacatgtcta cactttatga
81351 aaagtagtat taaagggaaa ataaagaaat ctttcctaaa tgatcttaca
81401 cagcagaaaa aaattagaag ttacaaatga cttaagttgt tctggattta
81451 gaaatggagg ggcattttta taacacctaa atggagggaa atgttgttta
81501 aatctataaa ccagatcaca gagaccaggt ttttataaag cttagtttgt
81551 acaatcacaa cctgtatgag atagagatct tagacagcgt aagacagtca
81601 ctgaaaagga gagatggaaa acagaacctc tgatgtaatt tctaatttca
81651 tagtacagtc atttatacta attaataatg gagtagatca ttgctcacga
81701 gtagcaaata gtattatcag accactgcat atttaaaaca tgattgcatt
81751 acttattgtc tggttattgt cactgatgta ctcagaagtg tggaatctca
81801 agataagaag gaaggttaaa ggttatctag agcccaaaaa tatctcagcc
81851 aagttgttat tcagttgaga cttaacacct tctagaaatg aaaaacccac
81901 cacctctcca gacagcctat agcatctttg aaccatcttt gagctactct
81951 aaaaataaaa agaaaagaaa agcaaccatt ccttacctgt agcaaatact
82001 gacttagtgc ttataaaatg tccatctcta acgaaagggt tagactcctt
82051 gaagtttaat aaaaaactaa taatttatag ctagcaagta aaatccacag
82101 acttgaaagc agcagagctc ccagccccat gctaataaac tcaagagtta
82151 aagacaaagc ccagagactg aatttagcaa gctccaaaag ccaacccaag
82201 gctgagacaa agcatcttgt ttttacaaat gttagtagac cagagcaaat
82251 tgaaaagagt gggggacatc aaagaaccag aattttggca gatcaagatg
82301 ataagcagaa gaaaagcaaa ctggcccaaa actaatgtaa acctagaagg
82351 gaatactaat cttactaatc ccaaaaactg aataggtgag ccaaaataaa
82401 aaaggcaagg aatggtaaaa gtgtgaatta aaatgggaat gtgctttgca
82451 atgatccacg ttcttgtctc tagtgtacaa atgggcaaaa tagaaaacct
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82551 cttttagtag gtgtacagtt ataacattat aaagaactac agctgggaca
82601 gattttatac agtcctctct cctccatttc atgaatagag aatctaactt
82651 tcagagtctc atcaaagtgc tagaagtatt cccatgttca cagcagtgag
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82801 aaaaagaaat gtcacagaga aggccacaca cacaaaaaaa aattttattg
82851 tgattttatt tataatcatg gtgcctatgc tataccacaa aagataataa
82901 atgacaatgc ctaattgact tactaaagaa cagaagttgt atctcctggc
82951 agtattgccc aacaatttgc cattggctat tggtattata atggagataa
83001 atactgctta ttttaataag taacatgttt atggacaggt tacataccgt
83051 ttgtcttctc tcagactcat tttagtgact ttttaatatt tgtattattt
83101 aacagtgctt ttgaaatttt tgagtgccat ttttgtattt tgttccagGG
83151 CATTCTTGGC TCAGGTTTTG CATTAAAAGT ACAAGAACAA CACCGCCAGA
83201 AACACTTTGA GAAAAGAAGG AACCCAGCTG CCAACCTCAT TCAGgtaaat
83251 gtcaatgtaa taggtagatg gcaacatttg tgtccatagt gcttgatggg
83301 tcattttcca atctctgtgc ttcattgctt ggtagaacta ctgctttgtt
83351 ccttttcata aaatgaagtc agaacttaat gtacagtctt ggatttggac
83401 agtcttggat ttgttcctcc tctcccaaac tgaaacacat gtatttttag
83451 caaatggtcc atgcattgtt cagactaagt aaccatgtca gcaaggccat
83501 gcaaaggtta gcagttgtgt ggctcgtgga attatctaat atgtcttatg
83551 aattacttga tgaaacgtaa ttgatcatta agtgatggag cagaacaggg
83601 cattgttccc tgcattccaa ttactttctc cagccagatg tatgttgctg
83651 ttttaaagaa caacatattt gtttagaatg tcaaggttta atacctgtga
83701 aattgctttt agtgccatct agggcagtta gcggaaatag ctatcctatt
83751 ttgagagctg atgggactat ggaatacatc agtgtttgag aatattaaac
83801 aataagtata taatttgaag ctagctccta atacataggt tgttatttag
83851 tatttcattt tcttttcact aactcaggat tagcttcagc actaaaagga
83901 atgcttctcc ttttgccatc catatatttt ccatcctaga tccaggttaa
83951 gaatcacaaa atatattttt tgttagattc ataatgtaga gttgacattt
84001 agttatggac aaaataattc tacaatctaa agtttctccc ctcctgctag
84051 ggaagtggaa gctaccgaat ttctaaactg gagggtcttg aagtggtgct
84101 ccaaggccct aggaaacttg ccttaaagct gcagtaacgg gcacactgtt
84151 ttgttgctgt tgttgttttg ttttattttt tgtttgtttt gttttttttt
84201 ttttgagaca gagtcgcgct ttgtcgccca ggctggagtg cagtggcgcg
84251 atctcggctc actgcaagct ccgcctcccg ggttcacgcc attctcctgc
84301 ctcagcctcc cgagtagctg ggactacagg cacccgccac cgcgcccggc
84351 taattttttg tatttttagt agagacaggg tttcaccgtg ttagccagga

Exon 7(C)

FIGURE 1AB

```
84401  tggtctccat ctctcaacct cgtgatccgc ccacctcggt ctcccaaagt
84451  gctgggatta caggcatgag ccacggctcc cggccacaag cacactgttt
84501  taatttagat tgtaggtttg ggtgggtggg ttggtgggag ataaccacca
84551  caacccctac ctttagtgtt gatctgtgac tgtgatatat gcagtgcctc
84601  ccacagacat ggagctgggg aaagaagggg gcagtatggt tcagttatat
84651  catgaaggag atctgtttat atctaatcat taaatgagga tattaatttt
84701  taaatcaagc tattctccaa ctgttgacaa gaaagtagac catcaggcat
84751  gacttccagt gcaaatcact gagaatctct atttttttac attatttttt
84801  acaatttttt tttttacat attctttaca ggttttaaaa ggtcactaaa
84851  gagaaagtaa actctatttt cttatatgaa gttggagttt aagatctgat
84901  gccaaacaat aatcagcaga atgaaaagag gagtcacaca ctttaggaca
84951  cacgcaaaat accccaaggt ccagaattca taggctttca tcctttagca
85001  ctccttaact ggttacacat gttccaatac ttctaataag tttttctctt
85051  tactgttctt atcctttaat tttccttcac tctagaacaa cgttttccaa
85101  cctgtgagtg cagaagttat tgcatgggtt cctttcatcc gtctgagcac
85151  caagctctgt ctacatatgg aaccaataat acattttaca caataaaacc
85201  tcttggaata tcagctgttt tgttagaaag tgagctcttt gaggaatttc
85251  tcatgcacat atcaattgtg atgatacaaa gctgtgccgc tcaatacagt
85301  aaccactagc tacatgtagc tttttacatt taaattaatt aaaattaaaa
85351  accaagtttg ccaatggcac tagccacttc tcaagtgttc aatagctaca
85401  ggtggctatc ggctgccata ccatacaaga gaaatataga gaataactgc
85451  aggaaatctc ctgatctaac ttgtcattat tgactactaa actgtgcaac
85501  aataatttcc aattgaactt gaaaataaat tgttatttct acagcaaatc
85551  attggagcag aggcatttat atgtctacag tcaaaatgag gcaaggcctc
85601  cctcacaggt aaccctgtgg aggacaggct aattgaacag ttttacttgg
85651  aggcctagaa ttttatttta tggaactggg ttatgtaaca tatattgtga
85701  tcagtaattg aacttgtaca aatgcaggta acaatgaagt aaaatcgtga
85751  gtttttattt tacttaaaac tccaacttaa atgttgttct taacaaaaat
85801  aatgcaaaat ggaatgcttg aagcattcaa gagtactttt aaaatctaat
85851  catagtttca ttaatcaaag tagaatctac taattttaaa agcaagtgct
85901  ccttcattta aatgcaatta atttattaca catagaaata ataatataat
85951  tattaatttg ttcattgttc ttccttgcta tagtctttag acagaattca
86001  aggctttaag ccttgattat atattataga aatttatatt tcaggatgta
86051  atagattgaa aagcaaactt catttaatca tcctttcacc ttcttaccca
86101  ataaacctga cttggtctgc tgaacacaca aaccatcaag cccaaaagcg
86151  tctcatttat tttaggccag agtcactgtc ttcttaaaag ggcaactgag
86201  atgcccaaat tgcttcatca tttggttggt gagagaacta aattaaccaa
86251  catttcaggg ttttaggaaa aaaatttaaa accccagaag cttgcagcaa
86301  atttagctgt gtcaatatct ttgcatgatt cttttaaatt tgcttttcat
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86451  aagtgctttt tagtttgcag ggtgcttcta atacattatg ttacttgatc
86501  ctcgagacaa gcctaggagg agctaggact caaatccctg ctgtctgaat
86551  ctgaatccat taccccttc aaaaagcagc atttacatcc tcataaatat
86601  atgctttatt agaaacagaa acagggaatt aagtaaaagt ttgtgaaata
86651  aatgttggta gggatagatt agaagatgtt gctttgatgc caactgaccc
86701  aaaagaaaaa tatatatatt tgtcttgaaa ctttggcttc ccctagtaaa
86751  atgacttagt ctccacccaa ttaccctaaa gcgaagccac tagtcattaa
86801  gctcaagcca cttatataga gattttacat ctttttagtg ctccagtcat
86851  aaataaaaac agtgccaggt gtggtgactc atgcccgtaa tcccagcatt
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87101  ttgaaaataa agcaaaaaag ataagaaaca tgaagtgtcc atccaggcat
87151  tccaatatcc agctaataaa gatgtctcag ctcaagtgca gggaaactaa
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87251  ggacaggagt ggccacagta gaagagctca ccaagtgtcc agcactgtga
87301  accaaaaact tcacaccaag attatcacag taaaatatca gaaaacttac
87351  caaaagggga tcctaaatgc tttctgagca ggacagagcc aaaggaacaa
87401  gaataaggat gacataggat ttctcattag taatccaaaa attagaagac
87451  aatgaaacaa tactttcgaa attatagaaa ttattttcaa cctagaacgc
87501  tatatccagc caaaccacca tcaagtgtga gagcagcacc aaggcacttt
```

FIGURE 1AC

87551 taggcatgca agatctcaaa aattaatcta ccatttacct ttactcaaga
87601 aactttgtaa atagaacttc tcttccacaa caaggggata agccaagaga
87651 gaaagagaca tggagtcaag aaaacaagag attccgcaca ggaaagagca
87701 aaggggattt ctatgataat agggaaggga agtcccaaga caacagctat
87751 gcaggccttg agaacagaat gagaaggagg ctgagagctc caggagaaag
87801 atcttcaagg aagcgaaaga atggagttct cagatttcat gatgcatttg
87851 accagaggaa ttttatagtt ctgttggaaa gatctggaat gtaatcataa
87901 caggtacata taggcaaatc aagaaattaa aatagggcaa ttataactcc
87951 aaaaaaacca aaaacttgta taagaaagaa agagcagcca tagtacatca
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88151 taattgataa tgtctaaaat tgaaaaatca agaaatataa ctataagcat
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88601 aaagtagtgt gaagaaagat gtggaaaggg attgctggtt catagcctaa
88651 aactttcagg actttcacat tttaaactct gtaccttgaa aaaataagct
88701 ctgtgttcat tattcctttg gatggtcagc tgaaacgttc taaaccattt
88751 ccagtaagga tcaaacatgc cataatggta atacttgcaa gacaaacaaa
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89251 gagtaatgaa gggaacaaga gcttagctgt tgggatcaat ctgagagaaa
89301 aatagcaaga catcaggtct cattgtaaag aaaatcttta attttctcag
89351 agtggcctct tttgccccca gttctttata acattcacag gcaatgcctt
89401 ggtcccattc ttttgttgtt ctgttgtttt ggattttttc actggtatct
89451 aataatgtgc agacctgcca tatgcttcta gttctacagg agtcttgctt
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90201 tagtattgta ctatgtaaat ggtgtcacaa attttctgtt tattctactg
90251 tttctgggta ttttggaatt tccagcttta gtttattaga aaccaacata
90301 tagtacatat cttttaatga acatatataa gcatatattt tgaaaatata
90351 cctaggagtg tgtagttgta tcataggata cttaaatgtt cagctttcgt
90401 agaaacttcc agttttccca agtagttgtg tgaattttta acttttattt
90451 agcatacatt tattcaatga tattctcagg aaaaggaata ttgttagatc
90501 acattttctt cattatggat ttcacaatca tgactgatgt gttatgtact
90551 agggatgtgg cccatttaaa tgaattggtc tgccaggcat ggtggctcat
90601 gcctgtaatc ccagcacttt gggaggccga ggtggcagat cacctgaggt
90651 gaggagttca agatcagcct ggccaacata gtgaaaccct gtctctacta

FIGURE 1AD

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FIGURE 1AE

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FIGURE 1AG

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FIGURE 1AH

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FIGURE 1AJ

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FIGURE 1AK

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116651 agcaggctgg gctggttcac atggtggtgg tgggttccca agagcagtac
116701 attgatatct gaaggcctct tgaagttcag gctcaaccta tcacagtata
116751 atgtccacta tgtcctgttg gtcaaagcaa atggcaagga cagcccacat
116801 gcaagagaca gagaaagaga ttccacctct tcatgtgaga agctgcaagt
116851 gtcgtggcca gtattgcaat ctaccatccc agccatttaa agcttatttg
116901 cttttagtat tttcaacatc ctgttggttc tatgaagaca gtgtcagtgt
116951 ctaattgact tttttatttc tccctgtagt atccttcact caaagagcct
117001 aagaaagaaa aggaaaatag cattgttagc acctcatgta tcgaggcatt
117051 ggctagacat tttctatgaa ttggctcatt taatacacac atagccattt
117101 tgcagataag gaaattgaga ctcagaaaat gtaaataact tgcccacata
117151 attcagtcta aatgccaaaa ctggggtttg aagttgcact taggtctaag
117201 ttcaaagctt tttatgttct accatgcatg ctgcttagca tgttttcttt
117251 catataattc atgctgctaa tgaaacagta taaaccagct gtatgttaac
117301 tgctagtgaa atgatttatt gtcttctttt tcagtaaata tggcaagtct
117351 gctcaattta ttccctttat cattgcatac actacaaata ttctctccct
117401 ataccttcac atgtcaatta aggtatgcaa cagtaatttc catttttttt
117451 aaacaatgct tatgttacca tctctagaca agttagtcca gatgattttg
117501 gggttaacat gttggcattt cctggcacta ttactgctag ctgaataaga
117551 gttgaaagtt ggggaaaaat ttaccagatc tgtattagtt ttttcgcaca
117601 ctgctataaa gaactacctg agactgggtg atttataaag aaaagtttaa
117651 ttgactcaca gttccacaac ctgtacagga agcacgcctg ggatgcctca
117701 agaaacttac agtcatgtca gaagagcgaa agggaaggaa gcgtgtcttt
117751 acgtggtagc agaagagaaa gagacagaga gaatgagaaa gtgagagtga
117801 agggggaagt gccacacttt taaaccataa tccaccccca tgatccattc
117851 acctcccacc cagtccctcc cccaacattg ggaataacaa ctcaacatga
117901 gatttgggtg gggatacaga gcgaaaccat atcaagatct atttagaatt
117951 ctccagcaga tttgattaac aatatagatt tgtgattctg caatttgtag
118001 ggtcattata aaacatggct gccttgattg caatcagata tctctgaata
118051 tggttcaaag gaaacagatc tcgttcttgt ggagatagga ttacataact
118101 ccctctcagt cattttgcca ttgattcaga atgtttctcc ctaagatgaa
118151 gtactgtttt agcttagaat ggtaacagca attcatcacc aggcacagtg
118201 gctcacacct gtgatcccca cactttggga ggcccaggcc tgtggatcac
118251 ttgagcccag gagttagaga ctagcctagg caacatggca aaaccccatc
118301 tctacaaaaa atgtaaaaat tagctgggca tggtggcaca ggcctatagc
118351 cccagccact tgggaggctg agaaatggga ggatcttttg agcccaggag
118401 gttgaggctg cagtgagcca tgatcgcatc actgcactcc atcctgggca
118451 acagaacaag tccctgtctc aaaaaaaaaa aaaaaaaaaa aaaaaaagca
118501 attcattgat ctcatctagt ttgactagtt caattataca tgtgagaagg
118551 ctatctgaga tgatgtcagg tgtggagcag tgactatccc agtgatctga
118601 atgtgattga ccacttggct tcaccaggat tatctcactg tttggttcta
118651 ataaaggcag tcattctagt ctatgagttt acctcccttt tgctacaaac
118701 acttcagtga tatactattg aaactataaa aatccataaa aattggtttt
118751 tgtatgtgag ttttaaaaaa ttgttttcac caggctgtga gttttatgtc
118801 tttgttttct attgggatac taatagtgct atgactatag tatgttctca
118851 aggaaattct tatgaaaatt gaattaatcc gacacagtgc atggttttgg
118901 agtaaaacag aacttgtttt aaatcctagt tcccccacta ggttgggtga
118951 gatgagacaa acgacttaac ctcactgcca ctttaatttg ttctctctct
119001 ctctttaggg tggtagaaat gatacctacc taatagggtt acgtgagtaa

FIGURE 1AM

119051 taataagata taatgtgtgt aaaattcttg tacaatgccc agcacagaat
119101 aggtgctcaa tatattaaat atattgttat tatttattaa ttaattaatg
119151 ctgatttctg cattaatttt gactaattga aatcctggac ttgcttaatt
119201 tgcatgtatt tgtcttccct tcttccagta cttgatggca atttctacct
119251 gtggtaaatg gaacgttaaa agttatatgc ttatacaaac tttagtcctt
119301 tattccttgg agtgagtttt aagagtcctc atgttgaata attcatgtaa
119351 tcacagaaat aatactatgt atcagggacc gcttccttta ttaaagataa
119401 aggcagtgga aatactgcct ttgtcagaaa tacttcagtt actctgagag
119451 agagagacat ttgtttacta tatgacagca cagtgcatgg caaataatag
119501 aagtttggaa aatatttatt ttgaatgaat gaataatgaa cacattgtga
119551 acaaataaat ggtttactat ttaattattc aggaatcaat taagctttat
119601 taataaaaat tgtttggggg ttttaaaaag cccacacaca aatgagaggc
119651 atcacagagg caaacggtat gacattatta aaatcgttat tgctgaatca
119701 cagttcagca ataagcaagt gtttgaggca ttcaaataag tgagtatttg
119751 agtgactcta agaagataat gaaactcctc cactgtttta cagttgcaat
119801 aatttttaag gaacatataa aaacatattc tagtgtttcc atttgaataa
119851 agatagtata tataacatat gcaattaaaa agaagaaaga aaacaaattt
119901 taatgtgttt ttcttttcac cttatgggca gttactagat gtat**nnnnnn**
119951 **nnnn**agcttc atcttgcccg tagaaaacag ttcagaaaag tattcatatt
120001 taaaactggg gaggctgtag aaaaagaaga aagaataata ttggcaagac
120051 aattggctga ccttatacat atcttggttt atcagcttac tctgtgagta
120101 tcccgccatt tccacgtgag aaaaattcag caacatgttt caaattgcgg
120151 atggtggtgt tatttaactg gcaatattct cttgcagCTG ACACAGCCCT
120201 TGGCACTGAT GATGTATATG ATGAAAAAGG ATGCCAGTGT GATGTATCAG Exon 11
120251 TGGAAGACCT CACCCCACCA CTTAAAACTG TCATTCGAGC TATCAGgttg
120301 gtgaaaatct tgaacaacgt gattcagaga catacttatg attaattgaa
120351 ttactatgtt gctaagttct ttttctgcag gtaaatatcc tggaataacc
120401 actttccctt tcctattcat **nnnnnnnnnn** aatagagtgt tttgcaaaca
120451 catttgtatc tcaaaaatgc atgtagttcc ataaaagacc attttaacag
120501 cctttatatt ttttaaggga tgctattact agataaagacc atttaacag
120551 ctggagattg catggaaaag ttagaattgc agatgttgta tcttggactt
120601 tcagggtttc aacggacatt aaaaaggcaa attttgactt taacttacat
120651 ttttttagtg tgtttttcta ttcttaaggt gttgtctcac atgagatgtt
120701 cttaaattgt ccactgtaat ctcaggcttt tatattacac atctgcagaa
120751 gccaaaaata atttgatgca tgacttttcc ccccagagtt tcttattata
120801 tttactggta aactattttg gtaacttata ttaacagagt tataaagatt
120851 aatatgtaat atgttctcat acagAATTAT GAAATTTCAT GTTGCAAAAC
120901 GGAAGTTTAA GGAAACATTA CGTCCATATG ATGTAAAAGA TGTCATTGAA Exon 12
120951 CAATATTCTG CTGGTCATCT GGACATGTTG TGTAGAATTA AAAGCCTTCA
121001 AACACGgtaa gcaatggaaa tgtcattcct tgtaaaggaa tgggcataga
121051 acctatctag gaagaacttc tctttagtag agtaaacctc tgaactccat
121101 atttttcatt catttttagt gggcaaatgg aatttgcttt aaacattgat
121151 tttattttgc ttttaacata gatataactc aggcattcaa agcatccaac
121201 tgtctcattt tccttatctg taaaaatggg aagaaagtta gttcttgcct
121251 tatagggttg tcatgaggat tgaacaagtt aatgcatgta attcataaca
121301 tgtaacaggc ctggtactgt gtctaataaa catcaatggt tgttgctgat
121351 gtttgaatta ttactgctgc tgatcctaaa ttatctaaat tccatttatt
121401 atctaaattc taatcatcct ttgggaataa cgtactattt ctccttcatt
121451 aagtttcatc caaccatcca acctgtgaag acgggccttt ctctgacctt
121501 tatacagtag cagagtctac tgcagagcac aagagcactc agaatctcgg
121551 tgtgctgggc caaagttgag acttggccct tgtgttgttt cctggttgca
121601 agtgtgttca ccttgctctg gactaagact gaggtccttc attcatgtcc
121651 tgtacggttc tacaaatata ctatcctcct agtagcatct tattgagtga
121701 ttaaaagaaa tgaattccac atgttaattc caaccacata tggttgattg
121751 tgattatctc aaagccaaaa tattcagtaa attcagtttt ttaagagcct
121801 tgctttatta ccagcacaaa ttaccagcat ttgtgattgt atagtgccca
121851 aaatgcaagg actgagactt gacttttttt tatgcccccc agcacactta
121901 gcccagtgtg aggcatataa tgggccctta gtaaaatacc tgttcatcaa
121951 ttgttataga aataacaatt tgttaattca tttagcaggt aattattgag
122001 cccatcatgt gtgccaggac ctgtggacat ccagagattg ataaaataat
122051 gacccagacc ttgtagagtt tgcagtttag taaattagat g**nnnnnnnnn**
122101 **n**gaacatctg aacatgacca gagattgtgg tcatattgca atctctgcct
122151 agatggccat ggccttctaa gttctttaat aaaactgtct acagctccca

122201 aggttttata aagttgaact gctacagaat ttatagaacc aatcttgggt
122251 ttctagctca tgtatcttct ccaacttgaa ctccgaaaga aaaagaccat
122301 ggctttctta tctgcttatc tttcacacat gtacaataga tgctcataga
122351 ataatctgtt ctattaatgt aagatctcta tagttatgat ttttgtcata
122401 ttttgaaatg gttaaattca ggaactgcct gatcagaggt agaaacatat
122451 tactttgtag tttaggacac ttttacttcc agaagatcac ccataagtga
122501 tttcatcttg gaccagaata atgagaaaat taatttcatg tgtaatctca
122551 tgttcaaata agcatatcaa ctggaacaag ttctttctta tttcatctta
122601 cataaattga agataactgt atttaatttt tttttccaaa actcttcatt
122651 ctgacctagg gcaatctcca ccttcagccc tcataatcag atctcctctt
122701 tctctgatag TGTTGATCAA ATTCTTGGAA AAGGGCAAAT CACATCAGAT
122751 AAGAAGAGCC GAGAGAAAAT AACAGCAGAA CATGAGACCA CAGACGATCT Exon 13
122801 CAGTATGCTC GGTCGGGTGG TCAAGGTTGA AAAACAGgta caactcaact
122851 acgctgggta tctttttagc cagaattttt ttaatcaaaa tttattatag
122901 gcaattgtat gtattccagt gattatttta aaataaataa aatcacaaaa
122951 agagtgaata aaattaaatt ttctttgtgt gtagacagtg ctctctgaaa
123001 cactctggat ttccctttaa ggaatagaaa atctcatctc atcaattaat
123051 agttaattgg aaacaactat agatttccaa tagttgaaaa tcgtttaaaa
123101 ataacaaaga tctattcttc atttgtgttt cagttgtttt tattgtttct
123151 tttttaggtc attaattttt tttttttttt ttt**nnnnnnnn nnn**gggacta
123201 tgggcatgca ccaccacacc tggctgattt ttgtattatt tttggtagag
123251 acgaggtctc accatgttgc ccaggctggt ctcaaactcc tgggctcaat
123301 tctcctgcct cagtttccca aagtgctggc attacaggca tgagccactg
123351 cacccagcct ggaatggaaa gtcttaaagt tgcattttta tagtgcttat
123401 atgactttta agaggcacta tttaaagaag tggtgggga gagatgctaa
123451 taaagactgt atagaagcca aagtgtccct ctcttcctaa gtcctcctct
123501 ggccccatca ttgctaaatg ttacattcac taagggtcaa gactgcatcg
123551 tactttatat tcaatatttc tttaaatgtg ttggcacacc ttgacttcat
123601 ttttcaaaat taaaaaatga agtccattct taataacaga ttatactcat
123651 gtgtaaccat tttcctcact tctagGTACA GTCCATAGAA TCCAAGCTGG
123701 ACTGCCTACT AGACATCTAT CAACAGGTCC TTCGGAAAGG CTCTGCCTCA
123751 GCCCTCGCTT TGGCTTCATT CCAGATCCCA CCTTTTGAAT GTGAACAGAC
123801 ATCTGACTAT CAAAGCCCTG TGGATAGCAA AGATCTTTCG GGTTCCGCAC
123851 AAAACAGTGG CTGCTTATCC AGATCAACTA GTGCCAACAT CTCGAGAGGC
123901 CTGCAGTTCA TTCTGACGCC AAATGAGTTC AGTGCCCAGA CTTTCTACGC Exon 14
123951 GCTTAGCCCT ACTATGCACA GTCAAGCAAC ACAGGTGCCA ATTAGTCAAA
124001 GCGATGGCTC AGCAGTGGCA GCCACCAACA CCATTGCAAA CCAAATAAAT
124051 ACGGCACCCA AGCCAGCAGC CCCAACAACT TTACAGATCC CACCTCCTCT
124101 CCCAGCCATC AAGCATCTGC CCAGGCCAGA AACTCTGCAC CCTAACCCTG
124151 CAGGCTTACA GGAAAGCATT TCTGACGTCA CCACCTGCCT TGTTGCCTCC
124201 AAGGAAAATG TTCAGGTTGC ACAGTCAAAT CTCACCAAGG ACCGTTCTAT
124251 GAGGAAAAGC TTTGACATGG GAGGAGAAAC TCTGTTGTCT GTCTGTCCCA
124301 TGGTGCCGAA GGACTTGGGC AAATCTTTGT CTGTGCAAAA CCTGATCAGG
124351 TCGACCGAGG AACTGAATAT ACAACTTTCA GGGAGTGAGT CAAGTGGCTC
124401 CAGAGGCAGC CAAGATTTTT ACCCCAAATG GAGGGAATCC AAATTGTTTA
124451 TAACTGATGA AGAGGTGGGT CCCGAAGAGA CAGAGACAGA CACTTTTGAT
124501 GCCGCACCGC AGCCTGCCAG GGAAGCTGCC TTTGCATCAG ACTCTCTAAG
124551 GACTGGAAGG TCACGATCAT CTCAGAGCAT TTGTAAGGCA GGAGAAAGTA
124601 CAGATGCCCT CAGCTTGCCT CATGTCAAAC TGAAA**TAA**GT TCTTCATTTT
124651 CTTTCCAGGC ATAGCAGTTC TTTAGCCATA CATATCATTG CATGAACTAT
124701 TTCGAAAGCC CTTCTAAAAA GTTGAAATTG CAAGAATCGG GAAGAACATG
124751 AAAGGCAGTT TATAAGCCCG TTACCTTTTA ATTGCATGAA AATGCATGTT
124801 TAGGGATGGC TAAAATTCCA AGGTGCATCG ACATTAACCC ACTCATTTAG
124851 TAATGTACCT TGAGTTAAAA AGCCTGAGAA ACCAAACACA GCTAATGCTA
124901 TGGGGTGTAT GAATATGTCA AGTTTAGGTC ATTTAGAAGA TTTGACACTG
124951 TATTTTGAAA TTATGGGAGT AAACACCTTC AAATTTCAGG CATTTCTGCT
125001 TTGTGACTAA ATACAAACTA CATTTTCAAG ATTAGGCCAT AATGTATATT
125051 TAAACACAAT GGCTATCAAC AGCTGCTAAT AAGGTATCAA CTAAAGCAGA
125101 ATTGGGGAAT AATAGAAATG GCTGCTTATT TCAAGATATA TTTGCCAACC
125151 CATTCCTATT CAGTCATTTT ATTATTAATG TAATTTGAAT GTCAATTTGT
125201 GTGCTTTTGG TGATTTAGCG CTGTGGCAAG CAATTTTGCA CATCATTTTC
125251 ATGTTGTTCT TTATGACAAG AATGTTCTTC AATTAGAAAA TGTGCAAATA
125301 ATGAAATTCA GGGCCAGTGA GGCAAATAGA CTATCTGACA TATTTGACTT

FIGURE 1AO

125351	TATGAAAACA	TATTGCCTGA	TGGCAGAATC	AACTTTATAA	GTGGTCAACT
125401	TCTACACAAG	CGTATGAAAT	ACTGGTCAGT	AGAACAGCCA	TTGTGATTGG
125451	ACTGGTTTCT	CTGCAATGGC	GCCAACCCCA	GGCTTGCCAA	TACTGCCTAT
125501	GTAAAGGGCA	AGTGTGAGAA	GCTATTCTCA	TTTCGCTGAC	ATACAGGTAG
125551	GACTATGGGG	GATGGGACAT	TTGAGTGGGA	CTGAGATAGG	AAAGGCTTGA
125601	AAAGAACCCA	GAAACACCAC	CAGGAAGTTG	GCAAAGTAAA	AGAAAATGAC
125651	TTCCCCCTCA	AAGGGCAATG	AGAGGGAGAG	AAACAAACCA	AAATAGAAGA
125701	ACTAGACTTT	TTAGAAAATG	AGTATTGCTA	GGGAATTCAA	CTACCTAATC
125751	TTCCCTTATT	CTTATATATA	AGCAGAGAAT	TTTTGCAAGG	TATTTATTTT
125801	TTAATATGCC	CTGAATGTCT	TTTGCTATTA	TGTGTACATT	TTGCATATGA
125851	AAGTCTAAAA	CGAAACTTCC	TTTACTTTTT	ATACTGTAGT	GAAAATTTTC
125901	TATTCTTCCC	AAGAATGTTG	TCCCAAATCT	GAAATTACTG	GTTCAATTTC
125951	CTGATATAAA				

FIGURE 2A

KCN6q cDNA

```
1   CTGGAGTGAGGCGCGGGAAGATGCCTGGTCCTTGCCTCGCGGACTTGGCA   50

51  GCCGCGTCCTGCGGGTCTGTCCACTGAACTGCTGAGGACTGCGGCGGTGG   100

101 CCTGAGGGAGAGCCGCCGGGGCAAGCAGGGGGCCCGGATGAGCCTGCTGG   150
1                                         M  S  L  L  G   5

151 GGAAGCCGCTCTCTTACACGAGTAGCCAGAGCTGCCGGCGCAACGTCAAG   200
6     K  P  L  S  Y  T  S  S  Q  S  C  R  R  N  V  K    21

201 TACCGGCGGGTGCAGAACTACCTGTACAACGTGCTGGAGAGACCCCGCGG   250
22  Y  R  R  V  Q  N  Y  L  Y  N  V  L  E  R  P  R  G   38

251 CTGGGCGTTCATCTACCACGCTTTCGTTTTTCTCCTTGTCTTTGGTTGCT   300
39   W  A  F  I  Y  H  A  F  V  F  L  L  V  F  G  C  L  55

301 TGATTTTGTCAGTGTTTTCTACCATCCCTGAGCACACAAAATTGGCCTCA   350
56    I  L  S  V  F  S  T  I  P  E  H  T  K  L  A  S    71

351 AGTTGCCTCTTGATCCTGGAGTTCGTGATGATTGTCGTCTTTGGTTTGGA   400
72  S  C  L  L  I  L  E  F  V  M  I  V  V  F  G  L  E   88

401 GTTCATCATTCGAATCTGGTCTGCGGGTTGCTGTTGTCGATATAGAGGAT   450
89   F  I  I  R  I  W  S  A  G  C  C  C  R  Y  R  G  W  105

451 GGCAAGGAAGACTGAGGTTTGCTCGAAAGCCCTTCTGTGTTATAGATACC   500
106   Q  G  R  L  R  F  A  R  K  P  F  C  V  I  D  T    121

501 ATTGTTCTTATCGCTTCAATAGCAGTTGTTTCTGCAAAAACTCAGGGTAA   550
122 I  V  L  I  A  S  I  A  V  V  S  A  K  T  Q  G  N   138

551 TATTTTTGCCACGTCTGCACTCAGAAGTCTCCGTTTCCTACAGATCCTCC   600
139  I  F  A  T  S  A  L  R  S  L  R  F  L  Q  I  L  R  155

601 GCATGGTGCGCATGGACCGAAGGGGAGGCACTTGGAAATTACTGGGTTCA   650
156   M  V  R  M  D  R  R  G  G  T  W  K  L  L  G  S    171

651 GTGGTTTATGCTCACAGCAAGGAATTAATCACAGCTTGGTACATAGGATT   700
172 V  V  Y  A  H  S  K  E  L  I  T  A  W  Y  I  G  F   188

701 TTTGGTTCTTATTTTTTCGTCTTTCCTTGTCTATCTGGTGGAAAAGGATG   750
189  L  V  L  I  F  S  S  F  L  V  Y  L  V  E  K  D  A  205

751 CCAATAAAGAGTTTTCTACATATGCAGATGCTCTCTGGTGGGGCACAATT   800
```

FIGURE 2B

206	N K E F S T Y A D A L W W G T I	221
801	ACATTGACAACTATTGGCTATGGAGACAAAACTCCCCTAACTTGGCTGGG	850
222	T L T T I G Y G D K T P L T W L G	238
851	AAGATTGCTTTCTGCAGGCTTTGCACTCCTTGGCATTTCTTTCTTTGCAC	900
239	R L L S A G F A L L G I S F F A L	255
901	TTCCTGCCGGCATTCTTGGCTCAGGTTTTGCATTAAAAGTACAAGAACAA	950
256	P A G I L G S G F A L K V Q E Q	271
951	CACCGCCAGAAACACTTTGAGAAAAGAAGGAACCCAGCTGCCAACCTCAT	1000
272	H R Q K H F E K R R N P A A N L I	288
1001	TCAGTGTGTTTGGCGTAGTTACGCAGCTGATGAGAAATCTGTTTCCATTG	1050
289	Q C V W R S Y A A D E K S V S I A	305
1051	CAACCTGGAAGCCACACTTGAAGGCCTTGCACACCTGCAGCCCTACCAAG	1100
306	T W K P H L K A L H T C S P T K	321
1101	AAAGAACAAGGGGAAGCATCAAGCAGTCAGAAGCTAAGTTTTAAGGAGCG	1150
322	K E Q G E A S S S Q K L S F K E R	338
1151	AGTGCGCATGGCTAGCCCCAGGGGCCAGAGTATTAAGAGCCGACAAGCCT	1200
339	V R M A S P R G Q S I K S R Q A S	355
1201	CAGTAGGTGACAGGAGGTCCCCAAGCACCGACATCACAGCCGAGGGCAGT	1250
356	V G D R R S P S T D I T A E G S	371
1251	CCCACCAAAGTGCAGAAGAGCTGGAGCTTCAACGACCGAACCCGCTTCCG	1300
372	P T K V Q K S W S F N D R T R F R	388
1301	GCCCTCGCTGCGCCTCAAAAGTTCTCAGCCAAAACCAGTGATAGATGCTG	1350
389	P S L R L K S S Q P K P V I D A D	405
1351	ACACAGCCCTTGGCACTGATGATGTATATGATGAAAAAGGATGCCAGTGT	1400
406	T A L G T D D V Y D E K G C Q C	421
1401	GATGTATCAGTGGAAGACCTCACCCCACCACTTAAAACTGTCATTCGAGC	1450
422	D V S V E D L T P P L K T V I R A	438
1451	TATCAGAATTATGAAATTTCATGTTGCAAAACGGAAGTTTAAGGAAACAT	1500
439	I R I M K F H V A K R K F K E T L	455
1501	TACGTCCATATGATGTAAAAGATGTCATTGAACAATATTCTGCTGGTCAT	1550
456	R P Y D V K D V I E Q Y S A G H	471

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1551  CTGGACATGTTGTGTAGAATTAAAAGCCTTCAAACACGTGTTGATCAAAT  1600
 472  L  D  M  L  C  R  I  K  S  L  Q  T  R  V  D  Q  I   488

1601  TCTTGGAAAAGGGCAAATCACATCAGATAAGAAGAGCCGAGAGAAAATAA  1650
 489   L  G  K  G  Q  I  T  S  D  K  K  S  R  E  K  I  T  505

1651  CAGCAGAACATGAGACCACAGACGATCTCAGTATGCTCGGTCGGGTGGTC  1700
 506    A  E  H  E  T  T  D  D  L  S  M  L  G  R  V  V    521

1701  AAGGTTGAAAAACAGGTACAGTCCATAGAATCCAAGCTGGACTGCCTACT  1750
 522  K  V  E  K  Q  V  Q  S  I  E  S  K  L  D  C  L  L   538

1751  AGACATCTATCAACAGGTCCTTCGGAAAGGCTCTGCCTCAGCCCTCGCTT  1800
 539   D  I  Y  Q  Q  V  L  R  K  G  S  A  S  A  L  A  L  555

1801  TGGCTTCATTCCAGATCCCACCTTTTGAATGTGAACAGACATCTGACTAT  1850
 556    A  S  F  Q  I  P  P  F  E  C  E  Q  T  S  D  Y    571

1851  CAAAGCCCTGTGGATAGCAAAGATCTTTCGGGTTCCGCACAAAACAGTGG  1900
 572  Q  S  P  V  D  S  K  D  L  S  G  S  A  Q  N  S  G   588

1901  CTGCTTATCCAGATCAACTAGTGCCAACATCTCGAGAGGCCTGCAGTTCA  1950
 589   C  L  S  R  S  T  S  A  N  I  S  R  G  L  Q  F  I  605

1951  TTCTGACGCCAAATGAGTTCAGTGCCCAGACTTTCTACGCGCTTAGCCCT  2000
 606    L  T  P  N  E  F  S  A  Q  T  F  Y  A  L  S  P    621

2001  ACTATGCACAGTCAAGCAACACAGGTGCCAATTAGTCAAAGCGATGGCTC  2050
 622  T  M  H  S  Q  A  T  Q  V  P  I  S  Q  S  D  G  S   638

2051  AGCAGTGGCAGCCACCAACACCATTGCAAACCAAATAAATACGGCACCCA  2100
 639   A  V  A  A  T  N  T  I  A  N  Q  I  N  T  A  P  K  655

2101  AGCCAGCAGCCCCAACAACTTTACAGATCCCACCTCCTCTCCCAGCCATC  2150
 656    P  A  A  P  T  T  L  Q  I  P  P  P  L  P  A  I    671

2151  AAGCATCTGCCCAGGCCAGAAACTCTGCACCCTAACCCTGCAGGCTTACA  2200
 672  K  H  L  P  R  P  E  T  L  H  P  N  P  A  G  L  Q   688

2201  GGAAAGCATTTCTGACGTCACCACCTGCCTTGTTGCCTCCAAGGAAAATG  2250
 689   E  S  I  S  D  V  T  T  C  L  V  A  S  K  E  N  V  705

2251  TTCAGGTTGCACAGTCAAATCTCACCAAGGACCGTTCTATGAGGAAAAGC  2300
 706    Q  V  A  Q  S  N  L  T  K  D  R  S  M  R  K  S    721

2301  TTTGACATGGGAGGAGAAACTCTGTTGTCTGTCTGTCCCATGGTGCCGAA  2350
```

```
722  F D M G G E T L L S V C P M V P K                                  738

2351 GGACTTGGGCAAATCTTTGTCTGTGCAAAACCTGATCAGGTCGACCGAGG  2400
739    D  L  G  K  S  L  S  V  Q  N  L  I  R  S  T  E  E               755

2401 AACTGAATATACAACTTTCAGGGAGTGAGTCAAGTGCCTCCAGAGGCAGC  2450
756    L  N  I  Q  L  S  G  S  E  S  S  A  S  R  G  S                  771

2451 CAAGATTTTTACCCCAAATGGAGGGAATCCAAATTGTTTATAACTGATGA  2500
772  Q  D  F  Y  P  K  W  R  E  S  K  L  F  I  T  D  E                 788

2501 AGAGGTGGGTCCCGAAGAGACAGAGACAGACACTTTTGATGCCGCACCGC  2550
789    E  V  G  P  E  E  T  E  T  D  T  F  D  A  A  P  Q               805

2551 AGCCTGCCAGGGAAGCTGCCTTTGCATCAGACTCTCTAAGGACTGGAAGG  2600
806    P  A  R  E  A  A  F  A  S  D  S  L  R  T  G  R                  821

2601 TCACGATCATCTCAGAGCATTTGTAAGGCAGGAGAAAGTACAGATGCCCT  2650
822  S  R  S  S  Q  S  I  C  K  A  G  E  S  T  D  A  L                 838

2651 CAGCTTGCCTCATGTCAAACTGAAATAAGTTCTTCATTTTCTTTCCAGGC  2700
839   S  L  P  H  V  K  L  K                                            846

2701 ATAGCAGTTCTTTAGCCATACATATCATTGCATGAACTATTTCGAAAGCC  2750

2751 CTTCTAAAAAGTTGAAATTGCAAGAATCGGGAAGAACATGAAAGGCAGTT  2800

2801 TATAAGCCCGTTACCTTTTAATTGCATGAAAATGCATGTTTAGGGATGGC  2850

2851 TAAAATTCCAAGGTGCATCGACATTAACCCACTCATTTAGTAATGTACCT  2900

2901 TGAGTTAAAAAGCCTGAGAAACCAAACACAGCTAATGCTATGGGGTGTAT  2950

2951 GAATATGTCAAGTTTAGGTCATTTAGAAGATTTGACACTGTATTTTGAAA  3000

3001 TTATGGGAGTAAACACCTTCAAATTTCAGGCATTTCTGCTTTGTGACTAA  3050

3051 ATACAAACTACATTTTCAAGATTAGGCCATAATGTATATTTAAACACAAT  3100

3101 GGCTATCAACAGCTGCTAATAAGGTATCAACTAAAGCAGAATTGGGGAAT  3150

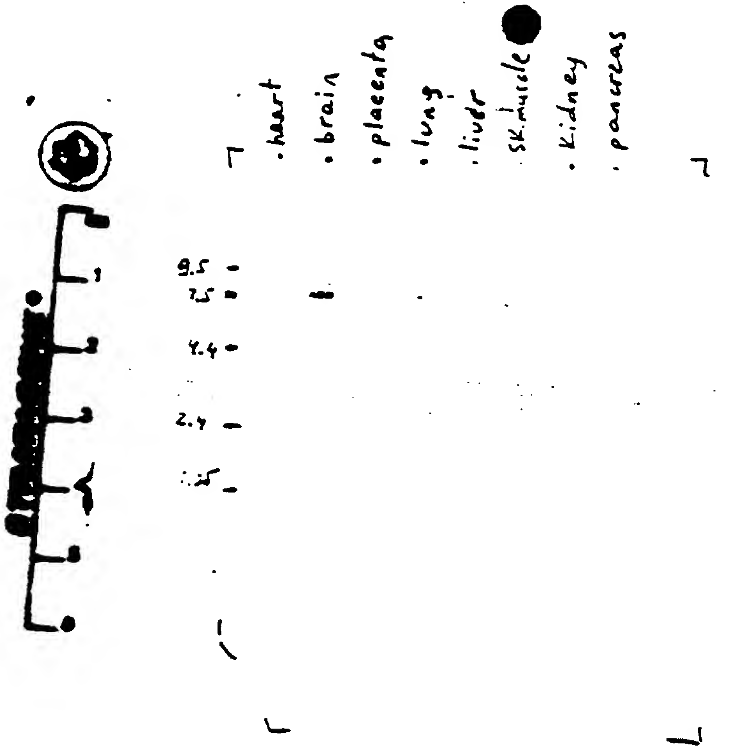
3151 AATAGAAATGGCTGCTTATTTCAAGATATATTTGCCAACCCATTCCTATT  3200

3201 CAGTCATTTTATTATTAATGTAATTTGAATGTCAATTTGTGTGCTTTTGG  3250
```

FIGURE 2E

```
3251  TGATTTAGCGCTGTGGCAAGCAATTTTGCACATCATTTTCATGTTGTTCT  3300
3301  TTATGACAAGAATGTTCTTCAATTAGAAAATGTGCAAATAATGAAATTCA  3350
3351  GGGCCAGTGAGGCAAATAGACTATCTGACATATTTGACTTTATGAAAACA  3400
3401  TATTGCCTGATGGCAGAATCAACTTTATAAGTGGTCAACTTCTACACAAG  3450
3451  CGTATGAAATACTGGTCAGTAGAACAGCCATTGTGATTGGACTGGTTTCT  3500
3501  CTGCAATGGCGCCAACCCCAGGCTTGCCAATACTGCCTATGTAAAGGGCA  3550
3551  AGTGTGAGAAGCTATTCTCATTTCGCTGACATACAGGTAGGACTATGGGG  3600
3601  GATGGGACATTTGAGTGGGACTGAGATAGGAAAGGCTTGAAAAGAACCCA  3650
3651  GAAACACCACCAGGAAGTTGGCAAAGTAAAAGAAAATGACTTCCCCCTCA  3700
3701  AAGGGCAATGAGAGGGAG
```

FIGURE 3A



probe: DL/ER PCR fragment.

FIGURE 3B

RT-PCR analysis of the KCN6q gene expression in human tissues

KCN6q cDNA
22 cycles

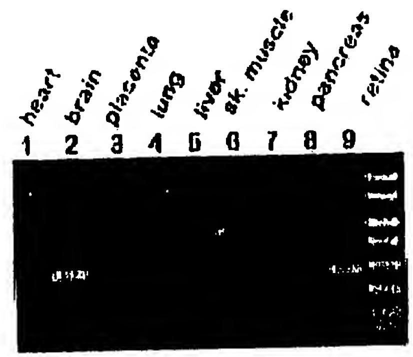


FIGURE 4A

```
KCN6q_     ......................................MS.....LLGKPLS.......
KCNQ4_     MAEAPPRRLGLGPPPGDAPRAELVALTAVQSEQGEAGGGGSPRRLGLLGSPLPPGAPLPG
consensus  maeapprrlg gpppgdapraelvaltavqseqgeaggg SprrlgLLG PL pgaplpg

KCN6q_     YTS.SQS.CR.RN...VK.YRRVQNYLYNVLERPRGWAFIYHAFVFLLVFGCLILSVFST
KCNQ4_     PGSGSGSACGQRSSAAHKRYRRVQNYVYNVLERPRGWAFVYHVFIFLLVFSCLVLSVLST
consensus   SgS SaC qR saa KrYRRvQNylYNVLERPRGWAFiYH FvFLLVF CLiLSV ST

KCN6q_     IPEHTKLASSCLLILEFVMIVVFGLEFIIRIWSAGCCCRYRGWQGRLRFARKPFCVIDTI
KCNQ4_     IQEHQELANECLLILEFVMIVVFGLEYIVRVWSAGCCCRYRGWQGRFRFARKPFCVIDFI
consensus  I EH  LA  CLLILEFVMIVVFGLEfIiRiWSAGCCCRYRGWQGR RFARKPFCVID I

KCN6q_     VLIASIAVVSAKTQGNIFATSALRSLRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT
KCNQ4_     VFIASVAVIAAGTQGNIFATSALRSMRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT
consensus  V iASiAVv A TQGNIFATSALRSlRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT

KCN6q_     AWYIGFLVLIFSSFLVYLVEKDANKEFSTYADALWWGTITLTTIGYGDKTPLTWLGRLLS
KCNQ4_     AWYIGFLVLIFASFLVYLAEKDANSDFSSYADSLWWGTITLTTIGYGDKTPHTWLGRVLA
consensus  AWYIGFLVLIF SFLVYL EKDAN eFStYAD LWWGTITLTTIGYGDKTP TWLGRlL

KCN6q_     AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAANLIQCVWRSYAADEKS.
KCNQ4_     AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRRMPAANLIQAAWRLYSTD.MSR
consensus  AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRR PAANLIQ  WR Y  De Sr

KCN6q_     .VSIATWKP...HLK.....ALH.....................................TCS
KCNQ4_     AYLTATWYYYDSILPSFRELALLFEHVQRARNGGLRPLEVRRAPVPDGAPSRYPPVATCH
consensus  a   ATW  yds L sfrelAL fehvqrarngglrplevrrapvpdgapsryppvaTC

KCN6q_     .P..TKKEQGEASSSQKLSFKERVRMASP.R..GQSIKSRQASVGDRRSPSTDITEEG.S
KCNQ4_     RPGSTSFCPGE..SSRMG.IKDRTRMGSSQRRTGPS.KQQLAPPTMPTSPSSEQVGEATS
consensus  rPgsT     GEasSS  s KeRvRMaS qRrtG SiK  A       SPStd   aEgtS

KCN6q_     PTKVQKSWSFNDRTRFRPSLRLKSSQPKPVIDADTALGTDDVYDEKGCQCDVSVEDLTPP
KCNQ4_     PTKVQKSWSFNDRTRFRASLRLK...PR..TSAEDAP.SEEVAEEKSYQCELTVDDIMPA
consensus  PTKVQKSWSFNDRTRFR SLRLKssqPkpv  Ad A gtddV dEK  QCdvsVeDl P

KCN6q_     LKTVIRAIRIMKFHVAKRKFKETLRPYDVKDVIEQYSAGHLDMLCRIKSLQTRVDQILGK
KCNQ4_     VKTVIRSIRILKFLVAKRKFKETLRPYDVKDVIEQYSAGHLDMLGRIKSLQTRVDQIVGR
consensus  lKTVIR IRImKF VAKRKFKETLRPYDVKDVIEQYSAGHLDML RIKSLQTRVDQIlGk

KCN6q_     GQITSDKKSREK...ITAEHETTDDLSMLGRVVKVEKQVQSIESKLDCLLDIYQQVLRKG
KCNQ4_     G..PGDRKAREKGDKGPSDAEVVDEISMMGRVVKVEKQVQSIEHKLDLLLGFYSRCLRSG
consensus  Gqi  DkK REKgdk   e E  DdlSMlGRVVKVEKQVQSIE KLD LL  Y   LR G

KCN6q_     .SASALALSSFQIPPFECEQTSDYQSPVDSKDLSGSAQ.NSGCLSRSTSANISRGLQFIL
KCNQ4_     TSAS...LGAVQVPLFDPDITSDYHSPVDHEDISVSAQTLS..ISRSVSTNMD.......
consensus  tSASalaLa  QiP Fe  e TSDY SPVD  DlS SAQt SgclSRS S Ni rglqfil

KCN6q_     TPNEFSAQTFYALSPTMHSQATQVPISQSDGSAVAATNTIANQINTAPKPAAPTTLQIPP
KCNQ4_     ............................................................
consensus  tpnefsaqtfyalsptmhsqatqvpisqsdgsavaatntianqintapkpaapttlqipp

KCN6q_     PLPAIKHLPRPETLHPNPAGLQESISDVTTCLVASKENVQVAQSNLTKDRSMRKSFDMGG
KCNQ4_     ............................................................
consensus  plpaikhlprpetlhpnpaglqesisdvttclvaskenvqvaqsnltkdrsmrksfdmgg

KCN6q_     ETLLSVCPMVPKDLGKSLSVQNLIRSTEELNIQLSGSESSASRGSQDFYPKWRESKLFIT
KCNQ4_     ............................................................
consensus  etllsvcpmvpkdlgkslsvqnlirsteelniqlsgsessasrgsqdfypkwresklfit

KCN6q_     DEEVGPEETETDTFDAAPQPAREAAFASDSLRTGRSRSSQSICKAGESTDALSLPHVKLK
KCNQ4_     ............................................................
consensus  deevgpeetetdtfdaapqpareaafasdslrtgrsrssqsickagestdalslphvklk
```

FIGURE 4B

```
KCN6q_    ...........................................................
KCNQ4_    MAEAPPRRLG....LGPPPGD....APRAELVALTAVQSE...............QGEAGG
KCNQ2_    MVQKSR........NGGVYPG.......PSGEKKLKVG....FVGLDPGAPDSTRDGALLI
KCNQ3_    MGLKARRAAGAAGGGGDGGGGGGAANPAGGDAAAAGDEERKVGLAPG..DVEQVTLALG
KCNQ1_    ...........................................................
consensus ma k rr  gaag gg  pg gggaa pag  al ag  er vgl pgapd    g alg

KCN6q_    .MS.....LLGKPLS...............YTS......SQS.CR.RN...VK.YRRLQNYL
KCNQ4_    GGSPRRLGLLGSPLPPGA.PLPG.....PGSG.....SGSACGQRSSAAHKRYRRLQNYV
KCNQ2_    AGS..EAPKRGSILSKP..RAGG.....AGAG...K.....PPKRN...AF.YRKLQNFL
KCNQ3_    AG....ADKDGTLLLEGGGRDEGQRRTPQGIGLLAKTPLSRPVKRNN..AK.YRRIQTLI
KCNQ1_    ..............................METRGS....RLTGGQGRV
consensus agspr a  lgspls gagr  gqrrtp gsgllakts s   kRnsaaakryrrlQnyl

KCN6q_    YNVLERPRGWA.FIYHAFVFLLVFGCLILSVFSTIPEHTKLASSCLLILEFVMIVVFGLE
KCNQ4_    YNVLERPRGWA.FVYHVFIFLLVFSCLVLSVLSTIQEHQELANECLLILEFVMIVVFGLE
KCNQ2_    YNVLERPRGWA.FIYHAYVFLLVFSCLVLSVFSTIKEYEKSSEGALYILEIVTIVVFGVE
KCNQ3_    YDALERPRGWA.LLYHALVFLIVLGCLILAVLTTFKEYETVSGDWLLLLETFAIFIFGAE
KCNQ1_    YNFLERPTGWKCFVYHFAVFLIVLVCLIFSVLSTIEQYAALATGTLFWMEIVLVVFFGTE
consensus YnvLERPrGWacfiYHafvFLlVf CLilsVlsTikeyeklasgcLlilE vmivvFGlE

KCN6q_    FIIRIWSAGCCCRYRGWQGRLRFARKPFCVIDTIVLIASIAVVSAKTQGNIFATSALRSL
KCNQ4_    YIVRVWSAGCCCRYRGWQGRFRFARKPFCVIDFIVFVASVAVIAAGTQGNIFATSALRSM
KCNQ2_    YFVRIWAAGCCCRYRGWRGRLKFARKPFCVIDIMVLIASIAVLAAGSQGNVFATSALRSL
KCNQ3_    FALRIWAAGCCCRYKGWRGRLKFARKPLCMLDIFVLIASVPVVAVGNQGNVLATS.LRSL
KCNQ1_    YVVRLWSAGCRSKYVGLWGRLRFARKPISIIDLIVVVASMVVLCVGSKGQVFATSAIRGI
consensus yivRiWsAGcccrYrGw GRlrFARKPfcviDiivlIASiaVvaagtqGnvfATSalRsl

KCN6q_    RFLQILRMVRMDRRGGTWKLLGSVVYAHSKELITAWYIGFLVLIFSSFLVYLVEKD....
KCNQ4_    RFLQILRMVRMDRRGGTWKLLGSVVYAHSKELITAWYIGFLVLIFASFLVYLAEKD....
KCNQ2_    RFLQILRMIRMDRRGGTWKLLGSVVYAHSKELVTAWYIGFLCLILASFLVYLAEK.....
KCNQ3_    RFLQILRMLRMDRRGGTWKLLGSAICAHSKELITAWYIGFLTLILSSFLVYLVEKDVPEV
KCNQ1_    RFLQILRMLHVDRQGGTWRLLGSVVFIHRQELITTLYIGFLGLIFSSYFVYLAEKDAVN.
consensus RFLQILRMvrmDRrGGTWkLLGSvvyaHskELiTawYIGFLvLIfsSflVYLaEKd    v

KCN6q_    ......ANKEFSTYADALWWGTITLTTIGYGDKTPLTWLGRLLSAGFALLGISFFALPAG
KCNQ4_    ......ANSDFSSYADSLWWGTITLTTIGYGDKTPHTWLGRVLAAGFALLGISFFALPAG
KCNQ2_    ...GE..NDHFDTYADALWWGLITLTTIGYGDKYPQTWNGRLLAATFTLIGVSFFALPAG
KCNQ3_    DAQGEEMKEEFETYADALWWGLITLATIGYGDKTPKTWEGRLIAATFSLIGVSFFALPAG
KCNQ1_    ....ESGRVEFGSYADALWWGVVTVTTIGYGDKVPQTWVGKTIASCFSVFAISFFALPAG
consensus daqge  andeFstYADaLWWGliTltTIGYGDKtPqTWlGrllaa FtllgiSFFALPAG

KCN6q_    ILGSGFALKVQEQHRQKHFEKRRNPAANLIQCVWRSYAADEKS..VSIATWKP.....HL
KCNQ4_    ILGSGFALKVQEQHRQKHFEKRRMPAANLIQAAWRLYSTD.MSRAYLTATWYYYD..SIL
KCNQ2_    ILGSGFALKVQEQHRQKHFEKRRNPAAGLIQSAWRFYATN.LSRTDLHSTWQYYERTVTV
KCNQ3_    ILGSGLALKVQEQHRQKHFEKRRKPAAELIQAAWRYYATN.PNRIDLVATWRFYESVVSF
KCNQ1_    ILGSGFALKVQQKQRQKHFNRQIPAAASLIQTAWRCYAAENPD....SSTWKIY......
consensus ILGSGfALKVQeqhRQKHFekrrnpAAnLIQaaWRfYatd psr dl aTWkyye  vtl

KCN6q_    K.........ALH.................................TCS.P....TKKE
KCNQ4_    PSFRELL....ALFEHVQRARNGGLRPLEVRRAPVPDGAPSRYPPVATCHRPGS..TSFC
KCNQ2_    PMYRLIPPLNQLELLRN.............................LKSKSGLAFRKDP
KCNQ3_    PFFRKE....QLEAA..................................S...........
KCNQ1_    ..IRKAPRSHTLLSP..................................S...........
consensus p frklp    L    qrarngglrplevrrapvpdgapsryppvatcsrpg aftk

KCN6q_    QGEASSSSQKLSFKERVRMASP.R..GQSIKSRQASVGDRRSPSTDITAEG.SPTKVQKSW
KCNQ4_    PGE..SSRMG.IKDRIRMGSSQRRTGPS.KQQLAPPTMPTSPSSEQVGEATSPTKVQKSW
KCNQ2_    PPEPSPSQKVSLKDRVFSS.P.RGVAAKGKGSPQAQTVRRSPSADQSLED.SPSKVPKSW
KCNQ3_    ......SQKLGLLDRVRLSNP.RGSNTKGKLFT........PLNVDAIEE.SPSKEPKPV
KCNQ1_    .PKPKKSVVVKKKKFKLDKDN..GVTPGEKMLTVP......HITCDPPEE..RRLDHFSV
consensus p epssSqklslkdrvrmsspqrgvgp gKl tap tmrrspstd t Eetsptkv ksw

KCN6q_    SFNDRTRFRPSLRLKSSQPKPVIDADTALG.TDDVYDEKGCQCDVSVEDLTPPLKTVIRA
KCNQ4_    SFNDRTRFRASLRLK...PR..TSAEDAP..SEEVAEEKSYQCELTVDDIMPAVKTVIRS
KCNQ2_    SFGDRSRARQAFRIKGAASR..QNSEEASLPGEDIVDDKSCPCEFVTEDLTPGLKVSIRA
KCNQ3_    GLNNKERFRTAFRMKAYAFW..QSSEDAGT.GDPMAEDRGYGNDFPIEDMIPTLKAAIRA
KCNQ1_    DGYDSSVRKSPTLLEVSMPHFMRTNSFAED..LDLEGETLLTPITHISQLREHHRATIKV
consensus sfndrtrfrt  rlkgsapr vqs edA  pgddvadek  qcdfsvedltpalk vIra
```

FIGURE 4C

```
KCN6q_     IRIMKFHVAKRKFKETLRPYDVKDVIEQYSAGHLDMLCRIKSLQTRVDQI
KCNQ4_     IRIMKFLVAKRKFKETLRPYDVKDVIEQYSAGHLDMLGRIKSLQTRVDQIVGKGQ.ITSD
KCNQ2_     VCMMKFLVSKRKFKESLRPYDVMDVIEQYSAGHLDMLSRIKSLQTRVDQIVGRG...PGD
KCNQ3_     YRIKQFRKYKKKFKETLRPYDVKDVIEQYSAGHLDMLSRIKSLQSRVDQIVGRGPAITDK
KCNQ1_     IRRMQYFVAKKKFQQARKPYDVRDVIEQYSQGHLNLMVRIKELQRRLDQSIGKPS...LP
consensus  irimkflvaKrKPketlrPYDVkDVIEQYSaGHLdmlsRIKsLQtRvDqivgkgp it

KCN6q_     KKSREK...............ITAEHETTD.....DLSMLGRVVKVEKQVQSIESKLDCLL
KCNQ4_     RKAREKGDK............GPSDAEVVD.....EISMMGRVVKVEKQVQSIEHKLDLLL
KCNQ2_     D..RTKG..............PAEAELP.....EDPSMMGRLGKVEKQVLSMEKKLDFLV
KCNQ3_     HKKSQKGSAFTFPSQQSPRNEPYVAR.PSTSEIEDQSMMGKFVKVERQVQDMGKKLDFLV
KCNQ1_     ISVSEK...............SKDR.GSN.......TIGARLNRVEDKVTQLDQRLALIT
consensus  kk reKg  ftfpsqqsprn p eaevp  seiedlsmmgrvvkVEkqVqsiekkLd ll

KCN6q_     DIYQQVLRKG.SASALALASFQIPPFECEQTSDYQSPVDSK...DLSGSAQ.NSGCLSRS
KCNQ4_     GFYSRCLRSGTSAS...LGAVQVPLFDPDITSDYHSPVDHE...DLSVSAQTLS..ISRS
KCNQ2_     NIYMQRMG...IPPTETEAY..FGAKEPEPAPPYHSPEDSREHVDRHGCIV....KIVRS
KCNQ3_     DMHMQHMER..LQVQVTEYYPTKGTSSPAEAE...KKEDNR.YSDLK.........TIICN
KCNQ1_     DMLHQLLSLHGGSTPGSGGPPREGGAHITQPCGSGGSVDPELFLPSNTLPTYEQLTVPRR
consensus  diymqvlrkg sas  lt aypqigafepeq sdyhspvDsk yvdlsgsaq  s tisrs

KCN6q_     TSANISRGLQFILTPNEFSAQTFYALSPTMHSQATQVPISQSDGSAVAATNTIANQINTA
KCNQ4_     VSTNMD..................................................
KCNQ2_     SSSTGQK...NFSAPPAA........PPVQCPPST....SWQ.......PQSHPRHGHGTS
KCNQ3_     YSETG..........PPE.........PPYSFHQVTIDKVSPYGFFAHDPVNLPR.G.GPS
KCNQ1_     GPDEGS......................................................
consensus  ts  gsrglq     ppe saqtfyalpp    q t   is     a  p n prng gts

KCN6q_     PKPAAPTTLQIPPPLPAIKHLPRPETLHPNPAGLQESISDVTTCLVASKENVQVAQSNLT
KCNQ4_     ............................................................
KCNQ2_     PV.GDHGSLVRIPPPPAH...ER..SLSAYGGGN............RASMEFL..RQEDTP
KCNQ3_     .....SGKVQATPPSSATTYVERPTVLPILTLLDS...........RVSCHS....QADLQ
KCNQ1_     ............................................................
consensus  p pa  gtlq  pp pa   lerp tl    ag  esisdvttclras e vqv q dl

KCN6q_     KDRSMRKSFDMGGETLLSVCPMVPKDLGKSL.SVQNLIRSTEELNIQLSGSESSASRGSQ
KCNQ4_     ............................................................
KCNQ2_     G.......CRPPEGTLR....D..SDTSISIPSVD.....HEELERSFSGFSISQSKENL
KCNQ3_     GPYSDRISPRQRRSITR....D..SDTPLSLMSVN.....HEELERSPSGFSISQDRD..
KCNQ1_     ............................................................
consensus  g   s r s r     tlrsvcpdvpsdt isl svqnlirsheelers sgfsisqsre

KCN6q_     DFYPKWRESKLFITDEEVGPEETETDTFDAAPQP........AREAAFASDSLRTGRSRSS
KCNQ4_     ............................................................
KCNQ2_     DALNSCYAAVAPCAKVRPYIAEGESDTDSDLCTPCGPPPRSATGEGPFGDVGWAGPRK..
KCNQ3_     DFVFGPNGGSSWMREKR.YLAEGETDTDTDPFTPSGSMPLSSTGDG.ISDSVWTPSNKPI
KCNQ1_     ............................................................
consensus  dfl     aa   fi  d  r yiaegetdtdsd  tp g  p satgeg  sdslwtg  k

KCN6q_     QSICKAGESTDALSLPHVKLK
KCNQ4_     .....................
KCNQ2_     .....................
KCNQ3_     .....................
KCNQ1_     .....................
consensus  qsickagestdalslphvklk
```

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/09587

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07K 1/00, 16/00; G01N 33/53
US CL : 530/350, 387.1; 435/7.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350, 387.1; 435/7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST DIALOG EMBASE MEDLINE BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	KANANURA et al. The new voltage gated potassium channel KCNQ5 and neonatal convulsions. NeuroReport. June 2000 Vol. 11, No. 9, pages 2063-2067, see entire document.	1-10
Y	WANG et al. KCNQ2 and KCNQ3 Potassium Channel Subunits: Molecular Correlates of the M-Channel. Science. 04 December 1998, Vol. 282, pages 1890-1893, see entire document	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 JULY 2000	04 AUG 2000

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	PATRICK NOLAN
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FIGURE 1A

KCNQ gene: DNA sequence

1. Underlined nucleotides in capitals represent exons.
2. Initiating ATG codon in exon 1 and terminating TAA codon in exon 14 are shown in bold italics
3. D6D280 genetic marker and phosphoglycerate mutase pseudogene are bold underlined
4. The exact lengths of the gaps between exons 1 and 2, 2 and 3, 10 and 11, 11 and 12, 12 and 13, 13 and 14 are unknown; these gaps are presented as runs of ten **bold n** as a convenience only

```
   1  CTGGAGTGAG GCGCGGGAAG ATGCCTGGTC CTTGCCTCGC GGACTTGGCA
  51  GCCGCGTCCT GCGGGTCTGT CCACTGAACT GCTGAGGACT GCGGCGGTGG
 101  CCTGAGGGAG AGCCGCCGGG GCAAGCAGGG GGCCCGGATG AGCCTGCTGG   Exon 1
 151  GGAAGCCGCT CTCTTACACG AGTAGCCAGA GCTGCCGGCG CAACGTCAAG
 201  TACCGGCGGG TGCAGAACTA CCTGTACAAC GTGCTGGAGA GACCCCGCGG
 251  CTGGGCGTTC ATCTACCACG CTTTCGTnnn nnnnnnnttc cttttctatt
 301  cttattatta atatatgatc ttattattaa taatataaag gaatagcaaa
 351  tgagaatcca tgagcaatat cagaccatga aaatgagcca gtggctgagt
 401  aacaaccaat taggacactt gatagtttag caaagttgcc aaacaggaga
 451  cagactcggc tcctttgaac gaagagtgac tgcagtgtgg attccccaga
 501  taggagagca agaacatact ttctgggcct ctctcaggat cgttgtttgg
 551  gaaggaagtt gtatgggaaa ttcacaaact cttagatgct aacatttaaa
 601  tgcagcatgc cacacacaca aacccacaaa cacaaccttt ttttcatcaa
 651  taaaattgca gaggagcccc atttgcacag tatatcacat tgtattttaa
 701  tatccaaaat ggctagtccc ttccagagtt tttatgagtt aatgtgtgct
 751  aatttaatgg gcctggtgct ttattcattt gaagcaagaa attaagtctg
 801  tgataataag gtaaggttct tatcagattt ctctttttgt tgttttacag
 851  TTTTCTCCTT GTCTTTGGTT GCTTGATTTT GTCAGTGTTT TCTACCATCC   Exon 2
 901  CTGAGCACAC AAAATTGGCC TCAAGTTGCC TCTTGATCCT Ggtaagtgaa
 951  acatgaacaa gaacgtacat gaatgttgta taagaactgc ctataacatt
1001  tatactatgc atcttatcct acaaaaaaat cctatctaaa aaagagttac
1051  tgagaaatat aaaaatgtca aagattactg aaacatttgc ccaccaattt
1101  aacatgtagt caatccttag aaatatatag aaatgttcag gattgctatt
1151  acacagcaat atcttgtgtt gtagatatat cataaataga aggcaatatt
1201  agaaagcagt tttaagtatg tttatctatg ctaataaaca aattatataa
1251  gaagaatcag tatctatgag gcctctcatt atattgtgaa agactataga
1301  gtagagagca ttttccaata actgtaattt ggcagtagct aaatataatt
1351  ggccaagaac tatgaacata tggcacctca taagaaaata gaaggctcct
1401  tcatgctctt ttcaaccaac agactgcatt atgagttttg ctgctaatgc
1451  agttacctgg tgataaattc tgcagtttgc tctgtttcca ttatgctgtc
1501  aatcctcaac cacacagaat tgctcaattc actttnnnnn nnnnnacgag
1551  gtcaggaggt cgagaccatc ctgcctaaca cggtgaaacc ccgcctctac
1601  taaaaataca aaaaattagc tgggcgtagc tactcaggag gctgaggcag
1651  gagaatggcg tgaacctggg aggcggagct tgcagtgagc cgagattgcg
1701  tcactgcact ccagcgacag agccagactc cgtctcaaaa aaaaaaaaaa
1751  aaaaaaaaaa gagtatactt gatttatggc atgagtggtc ttgaatgatt
1801  ttgatggatg actggaaaca attagagata taaataaata gcacagaatc
1851  atgacagatt tcatgaagaa tacactgtga agattcacat ggttaataac
1901  attgaaatta ttaaaataaa agagactgca tatattagat ttttctttgt
1951  gatctagttg ttcaaagcag cagaaaactt taaattttcc ttaattttga
2001  aagtgtgatt aatggaatat tgttacaatg ccattgattt atatactttg
2051  aggatagtta acttctttat gtttattaga aattgcactg agagctaata
2101  tgcagtttct attggtggtg atatgttctg ttaacagggc ctcctgtcag
2151  tttttattct gagatttctg cctttcctgt tcttttgcat gagcctaact
2201  gactgagttt caatatcaag ttctgaaagc aagtgagcat actagtgtgc
2251  atgcaatgtg cacagaaaga tgtgttttcc tacctctcaa agctcaccaa
2301  aggatattac tcatattgcc acaaagtaca tttacaccaa taacacatac
2351  tttggtaatg ggaaaaataa ataatcttag gtaataaaat gcactttggt
2401  gcttataaag gaaaataatc atcacaggta gaagaggagg aaggcaagac
```

FIGURE 1B

2451 taggttttga ttcaaaatgt tttctgtttt gctaggaagt ctagaaggaa
2501 tttggtcaaa tgacctgagg aggcaaggag atttctccca gtggcacatg
2551 gcagtccaca agaagactag gggcagggaa acaaagcaag attgtatctg
2601 atttctacag gactccaaca ctaccctgcc aataccottt tctcctctga
2651 aagccatgat cccaaaggtt tccatttctt ccgggttttt cacattctac
2701 caacaagcag aatgtcttcc ccactgacag ctcaacagtt gagtttttcg
2751 gggttctacc ccttcatcaa cacagccttt gctttcctgg ttactgagta
2801 aataaaacac actggccact tctgcttagc cttcaggagc cactctggct
2851 ccaccctgaa gttccatttc ctccaagaac taagacattt ggagattctg
2901 cctaaaatat gcttaaataa aagggataaa ctgtctctca ctttctttcc
2951 cccacagctt gtcttaagaa caacggtgta accattagtg aaaaatcctt
3001 tcaggctagt aaaatgtaaa aagagaagag gtatcgggta acaacaaatg
3051 aaaataaaat cattcagtgg tagaaaccat aggagtgaaa ttaggtagtt
3101 actgtcctcc agcttacatt aatcaaaata agcccacact gtcactaaga
3151 catcttgcag taagaagcca ttcaccctct cattgcaatt agtgtcataa
3201 agctgaatag acaggtcaga aatgaaaatc ataggccaat taagttattc
3251 tcatttttcc acctccagct agctcttttt gagaattttg attttaatag
3301 ataataaaac agtatgctaa ttgggtggtg ctgagcctga agccgtgaac
3351 tgaaggaaac ttcaacaaac atttggctag ggcctgctct aagcagaggg
3401 gctacgacaa tgggtaaggc atttctctag aaaccagcac tcagcagaat
3451 ttctggcacg agattttgtg agttttctag tggtgtgtct tatcttcccc
3501 caatagatta taaactcctc gagggtgaca gaacacattg ctgatcttta
3551 tatcctgcat gtttatggta ttcggtagac atttataaaa tgaattcatg
3601 aaaagcagaa catccagaaa tgaagtcaac attgcagaga agttagctat
3651 atgaaactct gtaaataccc tcaaggaaga aggaagaagc agatttctg
3701 gaaatcaagg gacctcccag tataagagca attcctttgg tcccaagaag
3751 ggcagctata agaacagaga cataactcct ccgtaagaaa agataaaaat
3801 tctgaaagtt ctctaagaac atgcccagcc ctgacctgcc tctcactctc
3851 agtagcatgg aagccgtact atctcttatc ttgacacaag catccacttc
3901 aatccacagg acaaatatca ccaatatgag aagataagat ctgttttata
3951 gtcaacttgg ctgacatgta ctaatttctc aaggtcagga tagctctcta
4001 aatagaaata cttgtttgtt ttaaggaatt ttatttaaat ttgtgtatct
4051 taaattttaa ttttgatctc ggctcactgc aacctccacc tcccaggttc
4101 aagcaattct cctgcctcag cctcctgagt agctgggatt acaggcacct
4151 gtcaccatgc ctggccaatt tttgtatttt tagtagagac cggatttcac
4201 catgttaacc aggctggtct caaactcctg acctcaagtg atctgcttac
4251 caaggtctcc cagagtgctg agattacggg catgaaccac tgctcccagc
4301 ctcatgtagt tcttaagagg aagaaaagcc tatagattag tgagaagtag
4351 acaaattagc aatttgaatc aaatgaaaac ttggtttgat ttcattcatt
4401 ttggagacac tttcggtgtt tccattttga tctgattcag gacactgatc
4451 ttcgattcta agttgcactg gttaatttgt gattatttta caaaatcata
4501 acagaataca tatctgggtc cagttcaagg tacagcaagc cattttcaat
4551 gtttccagct tggtgtttat gattcataca tgaatcattt gggcatgcag
4601 acacacccaa atagaaacct caaaccaatt aaggtataaa taggtttagg
4651 atgggggagg atggacaaca aaaaaaacct cagtaaggct cctccacaaa
4701 gggcaccact tcagcttggt cccatgggca gacttcacct gtggcaggtg
4751 aagggaaag cctaagacat cctgtgccct gatgcagatg tgacttacag
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4851 ggcaggcatt atagctgctg acaagagcca acccatccct aaggatctaa
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5001 gaatgtcctg ctgttcccac ctcttttccc caagcagggg gcacccactt
5051 cctgcctcca gcccatatgg tctcaattta tggcctcaat acctgataaa
5101 aaaccagccg tgatccttcc ttagtaacaa agtgtcaatc agtcatttgg
5151 aatgggcat tttcaaacta ttgcctccct atgatcttct gaagaacctc
5201 tgggataaat gaacattgtt atttaggtat ggttaaatga attactttcc
5251 aggagcagat ttatatatta acaggtgtga aaaacttgaa tggataaatc
5301 atttataaag aaatttcagg aatcaactaa tcccaagggg aaagacccac
5351 taagacacta gattttgctg gagctactca aacaaattca tctatcatat
5401 ctacctaagc cttccaatca atgagactag ccgcagtgac actgtctgtc
5451 aaaactacct cagtcatttt tttccaaggc aggaagcatc cataccoctt
5501 cacaccttaa tctaatttcc cctatctcca ccccactccc actttctatga
5551 ccccccttccc cccataccca cccccgaagc atctactagc caacttagtg

FIGURE 1C

5601 aagttctgtc acgctctcac aaccacctct gtgcagcaat gatttctgtaa
5651 atatccatgt gtcctcaaca ccaggtcaaa ttagtccctt tggtaaaaac
5701 attcattccc tcaaattctc ttccaataca ctaatatacc ttcccaaaaa
5751 gtaaggagaa gcttgaaagc tagctggatt gatgatggta tgtgatgttc
5801 tataagttat agttagtaag catgttttta ggatattttt ctgctctcca
5851 aagagacaca attccggaag atatttactt ttgtgtattt ccacattttg
5901 gtttaagttt ggagccatct ctagatctta atttcattcc cctaatatgt
5951 gttatactag tagaattttc caaattacat agaattataa ctgcaactct
6001 tctgactgat gccttttttt tgcattttat gatgcagttt acatcacaaa
6051 ttctttccct gcagggatta tgtaaagagg catgttgacc tgctagccct
6101 atgttacttt aagtatatgc acacacacaa aaaggaacaa aaacagctgg
6151 gaattgatta tgttgatatt ctgaataaaa gcaatagttc taattatgta
6201 tgtctaatta gccacagctc ttcaagaatt gctgcaaatg tcacaggtt
6251 tataatgtcg gcatttcatc ttcacgaaaa tgctatttga tggcataaaa
6301 ccagaaaaaa ctaatggtca cagaagacag cttgtagatt agacaaaggt
6351 cactgtgttt taatgaacag tgctgttaat taatgagaaa acaactggta
6401 catgagcttt taagcattgt gaatttgtac ccaaaaaatc aatctgccta
6451 aaacaatttt aagtagctaa aaaacaaaat aacggcaaga acataattta
6501 aacctcaaat ggtacagcag agttatatgt atcaattaaa ttgaatcaca
6551 gttctcaggt gtgacatatg aagaggcttc tttaatgcct ggaaaagagg
6601 gttaatatgg attggtattc tcaatacata ttgtagataa aattcaagac
6651 tagctctacc actgcctctt ttcttttttt tttttttttt ttatttgaga
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6751 tcactgcaag ctccgcctcc cgggttcacg ccattctcct gcctcagcct
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6951 tacaggtgtg aaccaccgcg cccggccacc actgcctctt aggcttctta
7001 atttccttat catttaagaa gaataagaaa atgcttctat gttttaccaa
7051 aattctgtga ggacaaatga ggaaccattg taactcctac aaggtgagtg
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7151 gccaagcttc taggggctta aataaggaag gacaggacca ttgttaataa
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7251 attattcact aatctcttta gctgccattt cagtaaatag cgagcatttt
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7651 ttcacatgca gttgtaagat atagtagaca taccctgtgt atactttacc
7701 caatttccgc aaaaggtaac attttgtaaa actatagtat aatatcacaa
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7851 tgtgtattgg ctctgtaaag ttttatcact tgcagagatt agtatatcta
7901 aaacaacaat caagatattg gacagttccg gccgggcacg gtggctcact
7951 cctgtaatcc cagcactttg ggaggccgag gcaggcagat cacgaggtca
8001 ggagatcaag accatcctgg ctaacacggt gaaaccacgt ctctactaaa
8051 aatgcaaaaa attagctggg cgtggtggtg ggcgcctgta gtcccagcta
8101 ctcgggaggc tgaggcaggc gaatggcatt aaccagggag gtggagcttg
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8201 actctgtctc aaaaaaaaaa aaaaaaaaaa gatatcggac agttccattg
8251 tcacaaggat ctctcaagtt acccccttgct aaccacatcc accttctcct
8301 tcacacttgc acaccccttc ccttctccag cctgacccca gcagccacta
8351 atctgttctc catttctgaa atgtttttat ttcaaaaatg ttatataaat
8401 ggaataatac agtgtataac tttttaagac tgactttttct tgcactcaat
8451 ataattccct ggcaattcat ttatgttact ctgtgtatca atagttcatt
8501 catttttatt attgagtagc attccatggt atgggaggcac cagagcttgt
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8601 attatgaata cttcttctgt gaacattcat gtacaggttt ttgtacaaac
8651 ataagttttc atgtctctga cacgaatgcc caagagtaca attgctgagt
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BNSDOCID: <WO___0061606A1TI_>

FIGURE 1D

8751	gaccatactg	ttttacattc	ccatcagcag	tgtttgaatg	atcccagcttc
8801	tccgcatcct	ccccagcatt	ttgtgttgtc	actatttttt	gccactattt
8851	tttattttag	ccattctgct	agctgtgtag	tgataccatt	gcgatctaat
8901	ttgcattttt	ctgatggcta	atgatgtcaa	ataacttttc	atgtgcttct
8951	ttgccatatg	tgtaacctct	tttatgtatg	tcctctttta	tgaatatcct
9001	atttatacct	ttgccaattt	tctaattgag	tttttggttt	tttactgttg
9051	agttttaagg	tttctttaca	tattttagat	attagtcctt	tgtcagatat
9101	gtggtttaca	aacattttct	cccagtctat	ggcttgtctt	ttcatcctta
9151	gtacctgggc	tctcacagag	taagttttta	cttttgatgg	agtccaattt
9201	ctcatttttt	ccttttataa	cttctgcttt	tgatgtcaag	attaagaact
9251	ctttgcttag	tccaaatccc	aaaaatatct	ccattttttt	cctaaaagtt
9301	ttattatttt	atgtttaatt	tttaaacccg	tggtccattt	ttaaatgatt
9351	atcataagat	aggaagtata	gattaaggtc	cactttttttg	cctatagatg
9401	tccaattttt	ccagcatcat	ttgttgaggg	cccttcttcc	tccattgaaa
9451	tgcttttgca	cctttaaaac	aaatcaattg	agcatatttg	tgtgggtcta
9501	gttctgaatt	ctctattctg	ttcactgttc	tatatgtctg	tatgttccat
9551	atgtctatcc	ctccaccaat	ccacagtctt	gattactgga	gccataatag
9601	taggctttaa	tatcaggtaa	agtgattgat	ctcgttttat	tctttctttgt
9651	cagcattgtt	ttagctattc	caggtcctgt	gcatttccat	ataaatttta
9701	aaataagttt	gtatctaccc	cccaaaaaaa	actttgctga	gattttgaca
9751	ggaattttat	tagacctgta	gatcaatttg	ggaagaattg	acatctttgc
9801	tatgatcagt	cttccaattc	ataaacacgg	tatttctcct	cacttattta
9851	ggtcttttct	gatttctttt	atctgcattt	catgatctca	atgcacataa
9901	accgtatgtg	tttttctaag	tggacattta	agttattttt	atttggaatt
9951	attataaata	ataattttgt	gtttctaatt	ttcatttcca	catgatcatt
10001	gttagtataa	agaaatatga	ttaattttta	tattgatcat	acatcgtgca
10051	gccttagtga	actcacttgt	ttcaagagtg	tcttcgtaga	tttcttggga
10101	tttttctgta	gaccatcatg	ccatttgtaa	atagagacca	ttttatgttt
10151	acctttccaa	actgcatggt	ttttttttctt	ttatttggct	tattgcagca
10201	actattaata	taacttacaa	tactatgttg	aataagagtg	atgaaagtat
10251	acatcttggt	tgttcttaat	gttggggaaa	agcattcagt	ctttcactat
10301	taagtatgat	gttaagtttg	ttgtaaatgc	tatttatcga	attaaactgt
10351	taaacctctt	ttcctaactt	gccaagagtt	ttttttaatc	ataaatgggt
10401	gttggatttt	gtcaaatgct	atttcgtcat	caatttatgt	gatttttttt
10451	tagctttatt	atataatgca	ttatattgat	tgatttcaac	cattgagcta
10501	gccttgcata	cctggaataa	atcctacttg	cctatatatt	gactgattga
10551	ctgtttgcta	atattttgct	gaggattttt	tgtgtctaag	tttatgataa
10601	atatgggtat	gtagtttttg	ttttgctttg	ttttattgtc	tttgtctggt
10651	tttggtgtca	ggataatact	gacttcataa	aatcattgag	aaagtttttt
10701	ctcctctatt	ttctgggaga	aattgtgtga	aaatgatata	ttcttattta
10751	aatgtctggt	tgattttgcc	agtgaaacca	tttgacctgg	acatttctgt
10801	ttggggagat	tttaaactat	gagttcaatt	gctttagcgg	ttatagggct
10851	acctagattg	tctatttctt	ctttgttgag	ttttggtagc	ttgtagtttt
10901	aaaggatttg	gtccatttct	tctaagttat	caagtgtatg	tgcgtaaagt
10951	taccatagta	ctccttcatt	ttttcagtgg	cgtagaatct	atactgatat
11001	ccccctattac	attcctgaca	ttggggattt	tcatcagctt	tcaagaaaga
11051	gatttatcaa	ctttattgat	ttttctcaagg	aaccactttt	ttgtttcatg
11101	gattttccat	attgttttcc	tcttttcagt	ttcattaatt	tttgctcttt
11151	tctatgttat	ttccttctat	ctgcttcctt	tgggtttatt	ttaccctttct
11201	ttttccaatt	tcttgaggta	ggtactcaga	ttattaatat	gagaactttc
11251	ttcatctaca	atgtaagcat	ttagtgctat	aaatttccct	ctcagcactg
11301	cttttactgc	atcctacata	ttttgttatg	tcattttttt	attttcattc
11351	agttcaattt	ttttaaaatt	tttgagactt	tctctttgac	caatggacta
11401	ctgggaatat	tgtttaattt	ccacatgttt	agagatttgc	ttgttgtctt
11451	tctgttattg	atttctagtt	ttattccatt	gtggcttgag	aacacattct
11501	gtctgatttt	attcttttaa	acttgttgaa	atttgtttat	gacccggaat
11551	ataatctatc	ttaataaatg	tgcatgggtg	ctttttaaaa	atgtgtattc
11601	tgctgatgtt	gggtgaaatg	tctcatatca	gtcagatcct	gcaggttgaa
11651	tgtgttgttc	aaatagttca	catacttgtt	aattttcatt	ctagtagtgc
11701	tatgcccata	gttctgagca	aggataaggt	gggttgatga	agttcccaaa
11751	tacgacttaa	catttgtcta	tttttccttt	cagccctatt	ggttttgctt
11801	tatgaatttt	gagactgtct	tgtcattttc	ccctcacctt	cttaaaaaaa
11851	aaagcagcaa	gcaatatttc	tgaacaatag	ggcttgaata	aagaacttgt

FIGURE 1E

11901	aaatgtactt	tatcctgcct	tactgcagca	gaggaatagt	gcagtgacct	
11951	tggcatacct	aagaacaatg	ggcatatatc	tgtcatttgt	taagaacaat	
12001	ggacatattg	gtgtcatctg	tttccatgaa	aaagaaaaat	tactacacag	
12051	tagtgttcgg	gggctcaggc	cacatttggg	attttcttgg	gatcccttat	
12101	aatatgagta	ctcacaactg	gagtgccaaa	tgtcctggca	taagcaggaa	
12151	ttagggcag	ggattaaaaa	gtggatctgc	cattcaacct	aggttgggca	
12201	caggcaccac	tacatgggca	ttttgggcct	gagtatgttt	tccatatttg	
12251	gaaagatgtg	ctggattaac	aagaaatgat	ctggcacttt	agatacctta	
12301	ataaatgaac	agactcaact	acccagatat	acattcaaaa	ccaaaacaaa	
12351	gccaaaatca	aacaaaacct	tcggattatt	aatgaatgta	tgttgaccct	
12401	aattttggtt	atctgtgcat	aaagtcatct	ttgaaggttt	atcctataag	
12451	taattttgaa	taactgtgag	taagcagtga	tgatattggg	tatttatttc	
12501	ccatcatgag	aaatatttgt	ggattactta	gtgcaaaata	agagaaggat	
12551	agaatgatat	agctctacta	ggcatttcaa	aagtgcagca	tatcatcaca	
12601	tgctctaatt	aaagaaacag	acatttgcct	gaaatttgca	acaaaaatgc	
12651	cacttttata	aatttggtaa	cagtttttat	cctgcgagta	agaatgggag	
12701	aatggggagt	aggttagaat	gtttactttc	tctgctttgt	atttctgtga	
12751	tgtttggaag	ttttaataaa	gacaatatat	tacttttacc	attaagctat	
12801	tataacaaca	atctataaat	attgttctac	attataaatc	ttgaatcaac	
12851	cctcgtttta	aaacaagaaa	gtgaattatt	ttttaaagga	aaaacaattt	
12901	tgataaataa	agtgcctgtc	cctatagaga	cagcaaggtg	actgtgctaa	
12951	gcttgctcca	gaaatgcttt	cgttttacaa	attccatttg	gtttttcatt	
13001	ctatcatcga	ctgtttaatg	agccactcta	gctggccttt	ccccagggtt	
13051	aactcacaac	tcttcctaaa	taatctcagt	cattttcctg	gagcaggtgt	
13101	tgttttctag	gcagctcttg	ccaaagggca	gcataataat	taacaagctt	
13151	cagatctgga	ggattcaggg	tctcatttct	ggcaaaggat	atgtgtgtca	
13201	cactgtaatg	cttttgaaac	ttactgtttt	ataaggagat	tttgacactg	
13251	taacgaaaga	attcagtata	cttcgaaata	tttgcttctt	tttctctaag	
13301	aacaactctc	gaagatttag	agattatgtc	actccttgca	gcaaaatgaa	
13351	gctctatttt	ctgtaaaact	tgccattata	tttcaggatc	gctattttat	
13401	ttcagatatt	tcacatgtta	ctgggtagct	aaagtcagct	acactataaa	
13451	ttccagacga	gacagatcca	ttattcagcc	tgcacattta	gtattgaaac	
13501	tgactcccaa	atttacgaag	cattaatgac	ttgaaaagga	atagcattcc	
13551	atgataggaa	atgcagacag	tatgaggttc	aaatgctgtc	cagatttagt	
13601	ttgatctgga	gaaaggaaat	gttcttaact	ttagatatta	acaactagat	
13651	cctttagaca	aagtgcctaa	atgtccaaaa	atatgcatag	agcttcttac	
13701	tgtggtttgc	tccataatgc	ttctctctga	tatgtcttat	ctgatatttt	
13751	agGAGTTCGT	GATGATTGTC	GTCTTTGGTT	TGGAGTTCAT	CATTCGAATC	Exon 3(D)
13801	TGGTCTGCGG	GTTGCTGTTG	TCGATATAGA	GGATGGCAAG	GAAGACTGAG	
13851	GTTTGCTCGA	AAGCCCTTCT	GTGTTATAGg	tgaatatcag	agtctcagat	
13901	acctggacta	tgacaccaac	attcttgtct	tctatctcct	gttttgcaat	
13951	atttgattaa	tattaaaagc	taacatccat	ggagtactta	tcatggaccg	
14001	ggcactcttg	tgtcttgaaa	atgttgactc	atttgatgtt	gtctccacag	
14051	cattatgagg	tagatatttt	tattatcccc	attttacagt	tgaagaattt	
14101	gagacaaaga	gagacggagt	tagttgctga	atgtcataca	gctactaagt	
14151	ggtagagctt	gaattttagc	caggcaatct	ggctctagaa	tacccactta	
14201	tatcaattaa	cttatatgga	aatacatgtt	tctccagtgt	tgccctaatt	
14251	taggggaaca	ttgatttcag	tgagtataaa	aaaccctttt	tgctctacaa	
14301	tatgacacca	gtttatgctc	tggatcagct	ggaatagata	gccatacatt	
14351	ggtactggta	atgcatatca	attaacattc	ttcaagaatg	attataagta	
14401	tggtttgctt	aatgcattgg	taactgtaga	ctggacaaag	tgctctacac	
14451	tctgaaatat	gaatccccca	ccctccaatc	caaatacccc	aaatacatag	
14501	cacatctctg	cacctcccta	gctgccattg	tttctgagag	acatcattca	
14551	cctgggttct	agcttgaaat	tgtacttcct	aatgaagatg	ccatagagca	
14601	ttctggaatt	aagatctagc	atttcccagt	aatatttaaa	agtattataa	
14651	aatggaaaag	tctatatata	aaagctatta	ttattattat	ttagtagcta	
14701	aatttggctc	tcttgctttt	ttgtctttct	cacttcctag	gcagccattc	
14751	aaatccaaat	actgaaaatt	cttgatgagg	cttatttatt	tcaactattt	
14801	tcaacctgaa	aaagtaggtt	tttaatttac	aaaacagttt	aggctatctt	
14851	ctacagctac	cacaggtttt	ctgttttgtt	ttaggagtca	ggaattgttg	
14901	cgtaatcttc	tcagtttcct	cccttactcc	tgttccctat	ggtgggggca	
14951	gagtggattt	aaggaagaaa	gtgtatcacc	atccatgggc	actgttaaga	
15001	agaatccttt	attccatact	tctttcatag	tatgcacatc	tcaaaagtct	

FIGURE 1F

15051 ccacttatta aaccagaatt tatggaaatg tggctgtgtg tgaggcactg
15101 gtgttacaat agtgaatcta gtggaattct cagttaaatc tatcttaaaa
15151 taccttgttt ggccctcacg aatgcagtct gtttgtctgt cttctccaat
15201 aataggcttt actgcttttt ggaagccatc atgctaaggt atggagcaaa
15251 gtcggtggta actccaagcc ttgcaggttc ataaagcccc aaggcatatt
15301 agtgaaggca ttagatcttt ctccctggag atgctttttt ctctctgaat
15351 tctctactca ggcagcatta caaaggactg taacctgatg tgaaactact
15401 gcacaacaag tactttctgt ccccataagg gccaaacaa aacaattcac
15451 aaggcagatg gttagccaag attcactcaa cttctacagg ataaggtcag
15501 ttcatggatg actggaaaaa tgtttcattc cagattttaa aaccaattaa
15551 aaattggttt tgttccaatt tcagaagcaa tgccaatgta tctctggcct
15601 ccatgcgaaa aagaaagctt tttcccagat gtctgctgcc ttttgatagc
15651 tgttttcagc tacggataca tcaacacatc ttagtccttt agtctttctc
15701 ttcctgcctc agatccttgc aggtcttgat ataatatgta gttctaaaaa
15751 tgatgttatg ttatctataa tcttacttgc ctttggatgt atcaatagtg
15801 accttaaaaa tttagtatga tgcctggcgc agtcactcct gcctgtaatc
15851 ccagcccttt ggaaggctga ggaaggcaga tcacttgagc ccaggagttt
15901 aagaccagcc tgggatggaa agacctgtct ctacaaaaat ttaaaaatta
15951 gctgggcatg gtggcataca cctgtagtcc cagctactca gaaggctgag
16001 actggaggat catttgagcc caggagtttg aggctgcagt gagccatgtt
16051 cctgccacta cactccagcc tgagtaaaaa gagtaagacc ctgtctcaaa
16101 aaaatactag tatgacatgg tttacgcata attgcagttt tgttaaccct
16151 tcagaccttt tctttattta gatattttac ctctaggaaa ttaattgctt
16201 tggaagaaaa tttcatggat aaatatataa tgaatcccca ttagaacaaa
16251 gtctagattt gtacttacag ttaggataat tatgaatttt ttagtctttt
16301 attaaatgta catgtttgac ccatggtcca gctgaatgga tgttatagtg
16351 aagcatgttc aaatgtggct tatcagtatg aggtcagtaa aatttaacct
16401 acacaaagga atcaaacatc accttcctga aggcagcaag ctgtaccaga
16451 tgactgttga gactatttct aggcccgttc aacaggttca taaaaacgct
16501 tgatgtaact ggtaaaatac taaagtgaac actgtagtcg ccttgttcaa
16551 cctaatttac tgtgacaaaa tgaaaaaaga aatagcatct cttatctgtc
16601 cctgataact gttctgaatg ggtgtttgga aatatagcta aaacctccca
16651 aaacttcatg tatttgtaag atttgattac tctgaacatt ccaagtacac
16701 acccaaatat ttttagaagt gttgagcatt cgagaaaaga acatagaaaa
16751 gattgtggta gactggctgt gccttcaacc tgggaaatgc tttctgtaag
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16951 tctgaactgc ccaccttcct taccccctgca ccctagccaa aaccaagagc
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17051 gtttggaaaa catattttaa acaattataa cataagggaa gaaataaatc
17101 tatttaactt tttttaatta ggtactttgt ttcattacta ctgtacattg
17151 atgtatgtct gcttggtttt aagcatttgc tttgaaaatt agtaaaatct
17201 tatctagaac ataaaattct tcctcatatc tatgtgttca atttttatct
17251 ctcccctaag actcttctgt cataataaca ttctatagct atgagcacta
17301 attgctgtat tgctgatgtg gatagtcaag tgtgttttgg gatgaccacc
17351 caagctgccc ttcatttacc cagactggct gctttatgat ttctctatgt
17401 gaaaacacaa aacactcacc caataacatc ggcataaaga atttgtgaat
17451 aacctctaag actgatttca tagtcattct tttttctagc tttcattact
17501 gacctacccca aaaattgcaa atagacctaa ggctgaaact tggatcacaa
17551 taatgagcct gatgtgtcag gaagccaaca aattacttct cacagtggct
17601 tttttagat tccttggtga cgctttccaa aggcagatat aacagggcca
17651 tatttttcag tcttgcaggg agtctcagtg agaaaatacc agcctgttgt
17701 tagtcttgga tctgcatttg atgctaagtg taagttgatt tcttattgtt
17751 attttaacag tttattttca gtgtaattat ttccacaaga ggacaaaaga
17801 ggaataaaat aaaattttat tttatcctac gtggataaaa taaaattgaa
17851 gcctttatta aaatcgacca catggctgag actactctaa tatatctatg
17901 atttcatctt attaaaaggc aacttaagtt gctaatgtgt tcaaaagtta
17951 gatcagactc ccaaaactgc cactgtgttc taaattgatt ttgagacatc
18001 atttttctgt ttctctgtct tctctatctt ttgttctaag agacttactc
18051 ttcaatggca ttatttctta taccttctac tcccttttcc ctttagtaga
18101 aattatatta tttcacttat tttctgttag tcatacactc tttctgcaact
18151 tattacttct aagtgttcaa actccctcag tgcatgtaga ttccttccat

FIGURE 1G

18201 gtgattaact ggaccatctg aggacaatta aaacctgttg gattggctga
18251 tcacaaaaca ttaaaacaat tttaatccct ctagttagta atagctgata
18301 tttattgaga actactatat attaggtact actttaagca ctttataaat
18351 atggtcttat ttaattctac ataagtacta taatgtcctt atttatttta
18401 ttttatttta ctttacttta ttttattcta ttttatttta ttttatttta
18451 ttttatttta ttttatttta ttttatttta tttttgagg cagagtttcc
18501 ctctatcacc caggctggag tccaaatggc atagtctcag ctcactacaa
18551 cctccgcctc ctgggttcaa gccattctca tgcctcagcc tcccgagtag
18601 ctgggactac aggcacacgc caccacaccc agctaatttt tgcattttta
18651 gtagagatag gatttcaccg tgttggccag gctggtcttg aactcctggc
18701 ctcaagtaat ccacccgcct cagcgtccca aagtgctggt attacaagtg
18751 tgagccacca cgcctggcct ttataatgtc ccattttata gatgaggaag
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18851 agatgatagg tgaaagaacc tggatttatt tctcatgatt tcactctaga
18901 aaaatataca tacccaactg gaaaattgtc tttactgttt attagcattt
18951 taaaattaaa tttaattgaa ccttatctat tgtcatcaac ttgtaaacag
19001 aagaacatga tactattatg cttatcatta gtaattcaag atctttaaag
19051 aaaagccagg ctttatagaa cattaattgc agtatcagcc ttaactatat
19101 caactaaatt atgttaccta ttgctgctct ctaacctgaa tgggaaatta
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19251 gagagcaagt aacattactc gcaggactac cttcaaatgt tttttaacat
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19451 ctttctataa actttagtag agcactatga tatactgtat taacattctg
19501 tactatcaca tgttacataa gaaaattcat tcacagacag ggtatttatt
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19651 aacttaaagg aggtatacta taattatggt gttacagagc aaaggtgatg
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19801 agtcatccac tgaacattta tacaatttct accatgtcca agcatgctta
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20351 gttgctggca ggcctaatat gaatactatt caggttatga acagcagcat
20401 taatcaggca acaaaaagta tggctgttta atgccctggg tttttagtc
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20551 aattttgttt ctatatttct gcccttagaa acatgaaatt ttacattgtt
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20701 ccttgccaag ggactctatt ccatactctt agttatgatg attgcagtgc
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20951 tttgaaaatg ttctacaagt ttgtctttgt ggtgcctttt ttatttttaa
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21151 tcaaagagca cctttctata aaggaatttg gagctcaatt agaatataga
21201 gcttataaag cagcaccatg tccctctgag acattgttta cttcactcta
21251 tagatggaaa agtcgaggca ctgtgaagtg gggtgcttt gtccttagcc
21301 cataaatcag cagtaaagct aggaatagca tgctggcctc ccaatagctc

FIGURE 1H

21351 attgctctaa agcactgcct cttgttagag tcaaatttaa ttatagtata
21401 atccgtttaa tctacatgtg gagaaataat gaaggagcag gaaaaatgaa
21451 tttcttaaca gatcagtgga aaaccatatt acatagatta gcaactgtct
21501 tttcaagatc cgtattttcg gcatgtacta gatggtatct gatgccatga
21551 aagcaaatat tctaattcca ctggccagaa ctggcaaaga acttcttatt
21601 ttcctcactt tgaaacataa gtaaaggggt tccacttgaa aattaacaag
21651 ccatgtgata tgattcgatt cctgtcccca aatctccctc cttctagggg
21701 ccattgtcta aagtctaaaa gaaaacatac caggcacagt ggctcatgcc
21751 tgtaatccca gcactttaaa gggagagcaa ggtaggagga tcacttgagc
21801 ccaggagttc aaaatcatca acctgggcaa cataatgaga ccctatctct
21851 acaaaaaaaa caaacaaaaa caaaaacaaa caaaaaaaac tgtaatagct
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22151 aaggaaggga gggagggaag gagggaggga aagaaaggaa aggaaagaaa
22201 ataaatgtaa ctattataaa agatgttcaa tgttttattt tggaataact
22251 ttagacttac ttagaagttg caaaaatagt acagaatttc catgttcaaa
22301 tgtactcttt acctaacttt ccccaaaata ttttacctac gtatactgca
22351 attatcaaaa ccaggatatg aatacatact attagctata gtctttattt
22401 gaatttcacc agtttttaca tgcgctcaat ttttatatac actcctataa
22451 aattttctca catgtatata tgcatttaac caccaccaca atcaaaatac
22501 aaaacttttc catcacccta aataaacttg gaatgatata ctttgtatta
22551 ttcctttaca ggtactccct ctcttcaatc ctaacctctg ggaaccacta
22601 tatctgttct gtttcactgt aattttgtca tttttataat gctatataaa
22651 tgaaattgta aagtagtaat cttttgaaat tggctttttc ttacacagca
22701 tgatgctctt gagatccatc caagtgcatc aatagtgcat tcctgtttat
22751 tgcttaatag aattccatga tctagatgta acacaatttg tatattcatt
22801 tacctaatca aggtcatttg ggctgcttct agtttttggc tattacaaat
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22901 tatttctcta gggtcatata gtgctagttc acctttatca gaaactgcca
22951 aactatttcc ttttaaaata tagaaatgcc aatgcaaaca tgtgcatgga
23001 ggtcagcagc cccaccccct gccccacgct gccactgctg ccagtgtgaa
23051 catatgcatg gaggctggca gccccacgct caccactagc ctgcccctgc
23101 actgacactg ctaccagcat gagcgtgcac atggaggccg gcagccccat
23151 ggccaccagc actctgcccc agttgatgag cattcacccc accacactgc
23201 cacttgctct tggcactgct cttggcactt acaaatgagc acagatcctg
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23501 aaaccttcca gggcatcaaa gaagatagag gcaaaaaaaa aaaaaaaaaa
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23701 cttaaccagg ctgaaatgac aaaaagagaa atcagaatgt ggataggaac
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23801 aggattacaa caaagtgata caggagatga aagacgaaat ggccacttta
23851 agaaagaaca gaactgatct gatagagctg aaaaactcac ttcagaatt
23901 ccagaataca atcacaaata taacggcaga atcgatcaag ctgaggaaag
23951 aatctcagag cttgaatatc gcttctctga aataactcag tcagacaaaa
24001 ataaagaaaa aaagattaaa gaagaatgaa caaaatctcc aaagtatggg
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24101 ggagagaaag caagcaactt ggagaacata tttcaggata tcatccatga
24151 aaattccccc aacttcacta gagaggccaa cattcaaatt gagaaaatgc
24201 agagaaccct tgtgagatac tatacagata atcatcccca agacacatac
24251 ttgtcagatt ctctaaggtc aaaacaaaac aaaaaatgtt aacagcagct
24301 aaagagaagg ggcaggccac ctcccaagga aaccccatca ggctaacagc
24351 acacctttca gcagaaactc tataagccag cagagattga ggacctatat
24401 tcagcattat taaagaaaag aaattccaaa caagaatttc atatccagcc
24451 aaactaagct tcataaatga aggagaaata agattctttt caggcgagca

FIGURE 1I

24501	aatgctaagg	gaattcatta	ccatcagacc	tgccttataa	gaggccctaa
24551	agagagtgtt	aaacatggaa	aggaaagatt	attactggca	actacaaaaa
24601	cgtgcttaag	tacacacacc	attgatgcca	aaaagcaacc	acacaaacag
24651	atctgcataa	taaccaatta	acaacacaaa	acaggatttg	atccttcaaa
24701	tccacacata	tcaatattaa	ccttaaatgt	aaatgggcta	aatgcccaat
24751	taaaaggcac	agagtggcaa	gttggacaaa	gaagcaagac	ccaacagtat
24801	gctgtcttga	atagacccat	ttcacatgca	gtgacgcaca	taggatcaaa
24851	ctaaagggat	ggagaaaaat	ctaccaagca	aatggaaaac	agaaaaaagc
24901	aggagttgct	attctacatt	caaacaaaac	agactttaaa	ccaacaaaaa
24951	tcaaaaaaga	taaagaaagg	cattacataa	tggtaaaggg	ttcacctcaa
25001	aaggccagac	ttaactatcc	caaatagata	tgcatccaaa	acaggagcac
25051	ccaaattcat	agagcaagtt	tttagacacc	cacaaagaga	tttagataac
25101	cacacaataa	tagtgggaga	ctttaacatc	ccactggcag	cattagacag
25151	gtcattgagg	cagaaaacta	acaaagaaat	tcaggacctg	aatttgacac
25201	ttgactaaat	agacctaata	gacatctaca	gaaatctcca	cccaaaaaca
25251	ggagtgtata	tattcttctc	atctgcacat	ggcccataat	ctaaaattga
25301	ctaatcagcc	ataaaacaat	ccttagcaaa	taaaaaaaaa	tcataccaac
25351	cacactctca	gactacagtg	caataaaaat	agaaattaat	ggaaattaac
25401	ctgcttctga	atgacttttg	ggtaaacaat	gaaattaagg	tagaaattca
25451	gaaattattt	gaaactaatt	agaacaaaga	tactacatac	cagaatctct
25501	gggacacagc	taaagcaata	ttaagaggga	agtttataga	gctgaatgcc
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25601	agaggaaata	gagaaacaag	agcagatcga	ccccaaagct	agtagaacac
25651	aagaaatcaa	aatctgcact	aaactgaagg	aaattgagac	gcaaaaaaac
25701	atacagaaga	tcaatgaatc	caggacttgg	ttcttcgaaa	gaataaataa
25751	gatagataaa	atgctagcta	gactaataag	gaaaaaaaga	gagatcaaaa
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25901	gaaaacctag	aagaaatgga	taaattcctt	gaaacataca	accttccaag
25951	attgaaccag	gaagaaattg	aatcctggac	agagaccaat	aatgagttcc
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26051	agagggattc	acagctgaat	attacaagaa	gtataaagaa	gagctggtac
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26251	aaaattctca	ataaaatcct	agtgaaatga	atccagcagc	acatgaaaaa
26301	gctaatccac	cactatcaag	gaggcttcgt	ccctgggaca	caagtttggt
26351	tcaacatata	caaatgaata	aatgtgattc	atcacataaa	cagaattaaa
26401	aacaaaaacc	acatgatcat	ctcaataaat	gcagaaaagg	cttttgataa
26451	agttcaacat	cccttcacgt	taaaaaccct	caacaaacta	ggcactgaag
26501	gaacatactt	caaaataata	agagccatct	ataagaaact	cacagccaac
26551	atcacagtga	atgagcaaaa	gctggaagca	ttcttattaa	acaccagaac
26601	aaaacaagga	tgtcctctct	caccagtcct	tttcaacata	gtactggaag
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26701	gaggggaagt	caaactgtcc	ctgattccag	tcagtatgat	tctatgccca
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26801	cagcaaagct	tcaggataca	aagtcaatgt	acaaaaatca	gtagaatccc
26851	tgtgcaacaa	caacatccaa	gctgagagcc	aaatcaagaa	tgctatcccc
26901	caagcctgcc	accatgggca	cctagaaaat	ggtgcagatc	cagcaaaggg
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27001	ctgagtccag	tggggcatgc	gggggaaaag	cagggcactg	gagatgctgg
27051	ctatgagttt	gagatctggt	tcacctcatt	gcagaagaga	gggatcccga
27101	gcttctggac	actggtagat	gccattgatg	agatggagct	gccaatagtg
27151	aggacttggc	gcctcaatga	gcagcactat	gggcctctgg	ccgctctgaa
27201	taaagcagaa	actggtggaa	aacatagtga	agcccaggtg	aagatctgga
27251	ggtggtccta	tgatgtccca	ccagctccga	tgggagccta	ccatcctttc
27301	taaagcaaca	tcagtaacga	tcacaggtat	gcagacctca	cagaaaatca
27351	cctaccgtcc	tgtgagagtc	tgaggcaaac	tattgccaga	gctatgccct
27401	tatggaatga	acaagtattt	cccaagatca	aggaggggga	atgggtactg
27451	actgcagcca	atggcaacac	cctatggggc	actgacaagg	atctgaaggg
27501	tctatctgga	gaggctatca	tggagctgaa	gctgccaact	ggcattctca
27551	ttgtctatga	attggacaac	aacttgaagc	ccatcaagcc	cagcccacag
27601	agttcatagg	ggatgaagag	accatctgca	aagccatgga	actgtggct

Phosphoglycerate mutase, processed pseudogene

FIGURE 1J

```
27651 gcccagggca aagccaagaa gtgaaggcca gcaaacaggc accctccctg
27701 cccattgcat ccatctgtcc ctccctcctg aacatgtcac actgaccaca
27751 tctatagaca tcttgagttg cagctgcaga tggggaccgg tggctcccat
27801 tttcatttta gccattttgt cttctgcacc cactcccttc atacattcta
27851 gtcagaatag cacttctagg gcacaggttc tcagtctaag ctgtggaaaa
27901 gcccccgtta tccaagagag ttcaaagata gtgacttggg tttttgcaag
27951 tgctttgttt actaaggact tgtgaggagg agccatgctg agctacgacc
28001 aatgaggaga agcaagagag cctgtctgcc cccaggagct agtcctgtgc
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28351 ctccttgacc tttgaggggc aggagtgctt catgctgtgt gttttagaat
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30751 agaaaaagga atgcttatat actgctggtg ggaatgtaaa ttagttcagc
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FIGURE 1K

```
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31051 aaaaagaaca agatcatgtc ttttgcaaca acatggatga ggctggaggc
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FIGURE 1L

```
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FIGURE 1M

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38751 catgatatac atgggacact aaaaaaatta taaatttctg cagaaaaggg
38801 ctcacattga taaggcagat tgacctctct gtctcaatct gctgtcccat
38851 tgggacaacc taaaatataa aaaacatgtt aattataata ttttcactaa
38901 attttacctg aatatcaact atttgcacgt agttatattc cctattcttg
38951 ataatacttt acttcttgga atatcacatg taagcctttg cttgactttc
39001 tacatccctg tttactaggc tttctatgac ataaaagcta ccaaagaga
39051 aacacgggaa aaaaatatat aagtgctctg gaaacagaaa ttagtttgat
39101 ttttggctcc atttaccagc taaatgactt tggataagat tcttggactt
39151 tcttagtatc aaattactaa tctagaaaag tgaagggaaa ggtatatcta
39201 taaaacattt tttttagat tgagagttaa catgatacca ggcacactaa
39251 ggcagactaa aggctttata tgtattattt catttaatca tcccaatagc
39301 cctgtgagaa aaagggatct attccctatt tgcaggtgag gactccaaga
39351 ctcagcaaga ttaataggcc caaggtcaca caactaagaa aggacagaac
39401 tagaaatacc tgggctgttg cacatgaagt ttatactcat aacctctgtg
39451 cctccttgaa gggctattat ggagaaacaa tgaaataaag tctgtgtact
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39601 gtactaacct ttctaggcca tagcttcttt tttaaataag ttatggttct
39651 ctttttctc attacaaaag caatacatgg ctattaaaga tcatttggac
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39751 cctaaagata atcaccatta atatgcaaat gtatgtattt atactattta
39801 tttttctata tactataaga atacataatc tggccaggtg caatgactca
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40351 atttttgcaa ccctatgaca taggtacctt tattatctac attttacaga
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40451 ctattaagca gcagagccag gattggaact gaggcacatg agcaccacag
40501 cccatgctct ggaagggata tagcatgttg tttttattta atccatcctc
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40701 tcctgaaata agttattcac attgttaatg gttttgtcaa ataatgtcaa
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41251 tactacaaac aaataactta tcaggtaagt atctatcaaa taagttttga
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41351 aaagcacctc tgcatgcagt tggtttctta tagcttacta tagaagagac
41401 cagcaagtaa acagactact agtataatca tgggtaataa gtgttatgac
41451 aggagcatac ctcagacctc tgggcacaag tggccttgac tggttgatat
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41751 ttgtagggat gaccaagaga gaagtagcgt agcctgaact aaggaggaga
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42001 tacgtttaca ataattgata ctactttgaa aaagaataac atttgtgtca
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42401 gttattcagg aacccaggct gacaaaggca gtgccatctt cagcacatgg
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43251 aaaattcatt aataagtgtc ttagtctatt tgttttataa taaaggaata
43301 cacaaagctg ggtattcata aagaaagtag gtttatgtgg ctcacagttc
43351 tgcaggctgt acaaaaagca tggtgcctgc atctgctcct ggtgagaacc
43401 tcaggctgcc tcccactcatg gcagaaggtg aagtggggcc aacatgtgct

FIGURE 10

```
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43551  caaggacggt accaagccat tcatgagcga tcctcccccca tgaccaaaac
43601  acctcccatt aggcttcacc tctaacactg gggatcacat ttcaacatga
43651  tatttggagg tcaaatatcc aaactatagc ataagtaatt ggttaattaa
43701  ataaattagt gtcctacctt atatacattt gtattgtttt gatattttac
43751  tttataactt taaagtgtat attttattaa aattattcaa aacttagctt
43801  atagtgaggc cactagaata attcaaaaaa ctggaacaaa aaaatgtggt
43851  gggagagggg gatataaaca tcaagaacat tgtatttgtc gtacttctga
43901  ttgtctcaga gagaacaaga tgaagtgagt ttaaagggaa agaggtaaat
43951  ttatgttagt tattagggaa aactttctga gactatagaa taacttttaa
44001  tttacaaaaa ttttaaaagc ctgaagtctc cagacagttt ctagaagtca
44051  agatatacce tctttgtggc ttacttacct cgagagggtt tatctgtcct
44101  tataactact agtttgaaag tgttcaacca tgctttgttt gatccagatg
44151  atttagttct tttcattgtg attttacatt gagccatgtt atactttcta
44201  atacatgcat tatgcagtgt aattgtagca acaaaacaca gtccatcagg
44251  ttcagatgta caattggcct tgctctaacc caatccttga gttcacaata
44301  gggaagcttt ggatgtaaat aatgaaggct ttttggtatt tcagtgacta
44351  acacctttta gacagggtcc atggtgatca attcatattg attttgctga
44401  ctaaataata cttgagcaaa gttccagtgg catctaaaaa taagctcttt
44451  cacagtcctt atgtgtctta aatatcatta tggtatttat tttgttcaaa
44501  tctttgcagt cacctcaaat ttcaagaatt catgtgtaaa tcattctaag
44551  tgatgcagta aattagtgaa cctacttcct aataccttgt aaacctatat
44601  ttcacatttc tactgggctg cttataatca atagctcttt cttcactact
44651  tcccaacttg ttctaatttg tttcctttga gagaggtaga ttttaagagt
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44801  gccataaaag taccatctgt ttttcagcat cattttattt ctgctttctc
44851  ctccctgcac ttttctcttc tctgaatgct ttatgcgata acaatttatt
44901  cctgatttat tatccacctg ctttcatagc ctcccccttt ctgttcctcc
44951  tccatcccta tccccaccctg gatggagtgg tataccataa ttcttaagga
45001  cacagctttg gagtcaagta agggccagct caaccactta tgcatgttag
45051  tgacttgacc actatgagcc tcaatttctt catttataag aaagagaagg
45101  ttataatatc atctactaca taggttggct tgaagaatta aataaaataa
45151  tgtacatcag ggtttctcag ccttggcact attgacattt ggggctgagt
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45651  ttaactaact gcacagctta agctactccc ccaatttaat atatatgcat
45701  atactttaaa taatagggag attttaaaat aaactctaat ggatgatagc
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45801  tttgattaac ctgagtattt taggttgata tcccagtcaa caagccattg
45851  atgtggtaag agaacaaagc tcagccaact tttaagtgtt ttttaatcta
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46051  atagaagtaa aaataaagac tactcataac ttgtaaaata ctagcctagg
46101  aaatagtcta ggtggtactg acagcaaaat tccagtggat gactgtaacc
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46201  catctatgat ttcagtttac tgaactctaa ctttctcgtc tgatctgaat
46251  tacaatgagg gtattaaatc aaatctgtgg ttacctttgc atatttttgga
46301  acttcaaaca tttagattgt gattcactgt gtgcataatt ttttaaattg
46351  tctcaaatca acaatctttc tcttactttt ctaggttttc tctaatgaac
46401  taactttata gcatactttt tgtgctgtag tctaacaaac cgatagctga
46451  gttttttttaa aaatgaatac aatatatgct ttttctgcct cgcttttttc
46501  atctgtaaaa tgggatctgt gggataccta acacataaag tcattgtaag
46551  gattaaataa ggtaatgttt attaaaaaaa aaaaaaacct tagaactgaa
```

FIGURE 1P

46601 gaaaatgcca agcacatagt aagttttaag tgtagtattt tctgcacccc
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46701 tgaggtagta tatctttttc ttttctttct acacttggga gaaagcagga
46751 ttacaatgaa ataaaagcaa aatgtatgtc caacagggtc atataagtaa
46801 tgtctgtttg taaaccacta gtctcaggag taaatccctc aacatgatga
46851 aaaccaagag atgtgtttgc acataactct ttttataaag tttttttaat
46901 tgcaaagaca tagtcgttgt tataaacttc caacatacag aaattaataa
46951 tttacaaagt gaaaagcccc tttatgcata tattcacttc agctcactcc
47001 ctttagaaat aattaatagt aataatcagc gtatagtctc actttttttt
47051 tttttttgag acgcagtctt gctctgtcgc taggctggag tgcagtggca
47101 cgatcttggc tcactgcaac ctccgcctcc tgggttcaag ggattctcat
47151 gcctcagcct tccaagtagc tgggattaca ggcacgtgcc accacaccca
47201 gctaattttt gtatttttag tagagacagg gtttcaccat gttggccagg
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48451 ctattataac aaatgtaata ttatttaatt atgcagcaaa cttacacata
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48851 tccaatctgt tgaaggttaa ataatacgtt gttcaaaatt gcataggtaa
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49151 TATCGCTTCA ATAGCAGTTG TTTCTGCAAA AACTCAGGGT AATATTTTTG
49201 CCACGTCTGC ACTCAGAAGT CTCCGTTTCC TACAGATCCT CCGCATGGTG
49251 CGCATGGACC GAAGGGGAGG CACTTGGAAA TTACTGGGTT CAGTGGTTTA
49301 TGCTCACAGC AAGgtaagat ttgctctctg aatttaaaaa cacaattttt

Exon 4(A)

49351 gaaacttttt cattgatcgc tgtaatagtt aataaacctg tcacaagaaa
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49451 atggattatt taagagccat cataaacatc caagaagtag taaagtgaat
49501 agaatcctca tagaattctt ttttcctttt tcaaagattt cccacctcta
49551 aaaatctttc attcctttta tatctagGAA TTAATCACAG CTTGGTACAT
49601 AGGATTTTTC GTTCTTATTT TTTCGTCTTT CCTTGTCTAT CTGGTGGAAA
49651 AGGATGCCAA TAAAGAGTTT TCTACATATG CAGATGCTCT CTGGTGGGGC
49701 ACAgtaagta taaaaataca ttttttattt actggatgtt gtgaattgtt

Exon 5(B)

```
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49801  taaattgcga aagagagtta tatggaaaat aaatactact tattattgtc
49851  taaaggcttt ccacatcttt ttaggccaac taagttgtct tgtaaaccat
49901  cattaatatt tcttgagtgc tagattgttg ccaaaattaa aaatatataa
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50151  aaccatctgt gagatcagag attatagtca cctaatttca aaactttcct
50201  ctcaaaacct actttttctt tatattatta aagaataatt ttccaaataa
50251  ataaagtaaa atcatgattc ttacatagaa agaaaattaa cacatgctaa
50301  acattcattt aactcatttt aaaagtttaa gtcattatta atgaagaaac
50351  cagtaagatg ttaaaaccag ttcaaagcac tatccaaagg acagaaacat
50401  ttaaagatca ggaatattga aatcaatgtg caaatagagg caaaactggc
50451  tccttccaca gtgtgggagg gaagtcagtt caacctccac taggcagaat
50501  ttatttacat gtccataggc aagaattatt ttgcattgct accagttatc
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50601  ccccataaaa tcagaatcca aaaacctgga agggtgtact ctgaacaacg
50651  catagttttc cactgaagca aaaatttccc ctgcattgta aagaatttat
50701  gaaacagtca ttggagctat gccgtaataa gaatgacatg ggatatagga
50751  gtgctttatg caatgtataa attacatttc tttttatttt attcctttaa
50801  ggtattccaa aggggagtta catgaaaata atcatagcca aacatggtgg
50851  ctcacgcctg taatccaagc actttgggag gctaaggcgg gccagttgct
50901  tgagctcagg catttgagac cagcctgggc aacatggcaa gaccccatcc
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51001  ccagctacct gggaggctga ggtggcagaa tcacttaagc ctggcaggta
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52151  gagagtaaaa attttataag agatcaaact tcgaagaatt ttttaaggcc
52201  ttattggtcc gtagcaggtt tgttgatatt aactgactca ttaatgaaat
52251  tgtctgaatc ctaaaaagac agaagaagca aacaaacaag agagctcatt
52301  gtttctattc attttaagaa gaacatatac tagattccta gtgggaaata
52351  aaataaattt agactattat acctttttatt tatacattaa tcaagacctt
52401  agtgaaaatt atggctgggt atttcttagt taaaattgcg catgttgcac
52451  ctaatggaaa ccttaataac tatggaagta tccagaataa atagggaaat
52501  gatagcatcc taaatgagag tatttctaag tgttacactt tgatgaaaaa
52551  aggaaatccc ctatattaaa agatcccaca gtatcaacat taagtatcaa
52601  aatataggtt ttgttccaca gatacgctgt gccagtgaat tttcaatact
52651  aactctggaa ctccttccat taagatagtg agatctgtcc cctagatcaa
52701  catttggagg gatatcatgg tgggatcagt gctgcccaaa aaactttgat
52751  ccctgaaagc agtttcatat tagtgaatag caatacctag ttcattgagt
52801  aagtgaaata gatataaaag acctggtacc aagaacatag gaagtgccca
52851  atcaaatatg agagctattg ttggtgtaga catcattgct gtggaagtta
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FIGURE 1R

52901	aatgaaagca	cctttaatac	aaaaggaaca	aaaaaagagt	tatgtgtttt
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53001	tgatgaaaag	atgtcctggg	ttctgatgtg	gcaactaaag	ttgcattgat
53051	ggcagaaaat	ggaagaggga	agtagctcta	gtagctgagg	cactgagagc
53101	tgctggaaaa	ggggatcttc	tgattgttgg	atagagctcc	atttattatc
53151	attttctatt	gttatttttc	tcattttttgg	ttgttccaga	tttattctga
53201	aataatttaa	gaatgggttt	ccctggagtt	attttctgtt	attaaatcct
53251	tcctgttttg	tgggagtgat	ttttctcttt	ttgatctgct	ttagatttat
53301	tttgaaataa	cttaagatca	ggtttttcctg	cactccagcc	tgggtgcttg
53351	agtgagaccc	tgcctcaaag	actcccttgg	ggagaattat	accgtgccac
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53451	aatgtacata	gatttactaa	aaacataatt	gtatcttcaa	aatcaggtca
53501	ataaatattt	gttgatttgt	tgcctgaaag	aaagaaggat	ttatatctcc
53551	tgatttggaa	ttaattctgc	tattgaaaag	aaaaaaaact	ttagcctaac
53601	cagtgtctta	aattataatc	tgaccatagc	ctcagccatc	tcatttaaaa
53651	aaaaaatcaa	gaaaagtctg	gaccagagtt	ttcatttgtt	tttcagtatt
53701	atttctgagg	aagaattcct	gaatgctaaa	cacacgaagg	tgccccccact
53751	ccacctcaga	ttttcctaac	ataattacaa	ctttatgcca	acatttccaa
53801	cccacagatt	ttcagaatgt	attttctttc	acctgtgtga	ctgtatttga
53851	gcataggaaa	cataagggcc	aaaatatatc	taagctgttt	ctatctgcaa
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55801	acccattaac	cgacccacact	ttagttcttt	ctgtcatccc	aaacccaccc
55851	aatccctgtc	atccccacct	acctagccca	tatgtagtca	tgaagcatcc
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55951	tcacccatgg	gactcaaccc	ttgcacccta	atgccatatg	cacatataga
56001	actggcagag	aattacacaa	caaaggggggc	gggatgtgat	ggaagtatct

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59151 atttgaggc ttctgacatg agcaagtgga tagattggtg gagctcttgg
```

FIGURE 1T

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59301 atgtgaattg ggaactcaga aaagtggtct ggcctagaga tataaatttg
59351 gagtgtttag cataaaagtg gcatttaaat ctatgagaac atttaagatc
59401 acctggaaag agagaaaaaa gaggggatag aaaagaaagg aaagtctaag
59451 aagaatacaa tttttaaaag aagaaaaaga cttagaacaa aaccttaaaa
59501 atccagtgtc caaaggttga aaagggtaag aggagccaca gaaaaagagc
59551 caccaaggaa tacaaagaga aaaccatgga agtgaagaga agagtgcttc
59601 tagaaagagg tggtcagctg agctgaatgc ttctgaaagg tctggcatca
59651 tagaatttgt ctccctcttt atcaaacctg cttctgaatt gttcccccctc
59701 tttcaaagcc caggtaaggt ggcatgacca gagcaaccac ttttcagtg
59751 attgccagtg accacctatc cccaccatat tcagtctctt ttttcaatg
59801 ctcatcgtcc ttgttttctt tttctctctc tctctctttt tttttttttc
59851 tttccagatg gagtttcact ctgttgccca ggctggagtg caatggtgtg
59901 atcttggctc actgcaacct ccacatccta gattcaatca attcccctgc
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62251 tttgtttttta ttgcattcac ttttgggttc ttggtcttga aatccttgcc
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FIGURE 1U

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64801  tggtatcaat tcttctttga atgtctagta gaattctgct gtgaatccat
64851  ctggtcctgg actttttttg ttggtaattt tttaactacc atttcaatct
64901  cattgcttgt tattggtcat tcaggctatc taattcttcc tgatttaaag
64951  taggggggtt gtatttttcc agaaatctat ccatctcttc tagattttcc
65001  agtttatgtg cataatggtg ttcatagtag ccttgaatga tctttttgtat
65051  ttctgtggtg tcagttgtaa tatctcccat ttcatttctt cttgagctaa
65101  tttgcatttt ctctcttctt tttatggtta atcttgctaa cggtctatca
65151  attttattca tttttaaaga accagctttt tgtttcattt atcttttgta
65201  ttttgtttgt ttgtttcaaa ttcatttggt tctgctctga tcgtggttat
65251  ttcctttctt ctgctgggtc tgggtttggt ttgttcttgc ttctctagtt
65301  ccttgaggtg tgaccttaga ttgtctgttt gtgctctttc agactttttg
65351  atgtaggcat ttatggctat aaactttcct cttagcatcg cctttgctgt
65401  gtcccagaga tcttgatatg ttgtgtcatt gttgccattc aattcaaaga
65451  attttttaat ttccatcttg atttcatttt tggcccaatg atcattcaag
```

FIGURE 1V

65501	agcaggttat	ttaatttcca	tatatttgca	tggctttgaa	agttcatttt
65551	ggagttgatt	ttcagtttta	ttccactgtg	gtctgagaga	gtgcttgata
65601	taatttcaat	tttcttaaat	ttattgaggc	tcattttgtg	gcctgtcgta
65651	tggtctacct	tggagaaagt	tccatgcact	gaatagaatg	tatattctat
65701	ggttgttgga	tggaatgttc	tgtatatatc	tgttaagtct	atttgttcca
65751	aggtatagtt	taaatccatt	gtttcattgt	tgaccttcag	tcttgattat
65801	ctgtccagtg	ctgtcagtgg	agtattgaag	tctcccacta	ttattatgtt
65851	gccacctgtc	tcatttctaa	ggtctgttag	taattgtttt	ataaatttga
65901	tagttccagt	gttcagtgca	catacgttta	ggattgtgat	gttttcctgt
65951	tggactaggc	cttttatcat	tatataatgc	cctctttgtc	tttttaaaat
66001	gctgttgctt	taaagtttgt	ttgtctaaga	acaggtactc	ccgtttgctt
66051	ttggtgtcca	tattccaaaa	atgtcttttt	ccacaccttt	accttaagtt
66101	tgtgagactc	cttatgtgtt	aggcgagtct	cttgaagtca	gcaggtagtt
66151	ggttggtgaa	ttcttatcaa	ttctgcaatt	ctatatcttt	taagtggagc
66201	atttaagcca	tttacattca	acgttagtat	tgagatgtga	ggtaccattc
66251	cattcattat	gctatttgtt	gcctgtatac	cttggttttt	tgttttttgt
66301	ttttgttttt	taaattgtat	ttttgtttta	taggtcctgt	gagatttatg
66351	ctttaaagag	gttctgtttt	gatgtgtttc	caggatttgt	ttcaagattt
66401	agagctcctt	ttagcagttc	ttgtagtggt	ggcttggtag	tggtgaactc
66451	tctcagaatt	tgtctgtctg	aaaaagactg	tatctttcct	tcatatatga
66501	agcatagttt	tgttggatac	aaaactcttg	gctggtaatt	cttttgcttg
66551	aggaggctga	agacaaggcc	ccaataccct	ctagcttata	gggtttctgc
66601	tgagaaatct	gctgttaatc	taataggttt	ttatttatag	gttaccaggt
66651	acttttgtct	cactgctcct	aaaactcttt	cctttgtctt	aactttagat
66701	tacctgatgg	caatgtgcct	aggtgatgat	ctttttgcaa	tgaatttccc
66751	aggtgttcct	tgtgcttctt	gtatttggat	gtctaggtct	ctagcaatac
66801	tggggaagtt	ttcctctgtt	attccctgaa	atatgttttc	caaactttta
66851	gatttctctt	ctttcctcaag	aacactgatt	attattagct	ttggtcatct
66901	aacataatcc	cagacttctt	ggaggctgtg	ttcgtatttt	cttattcttt
66951	tttctttgtc	tttatggagt	gggttaactg	aaagaccttg	tcttagagct
67001	ctgaacttct	ttcttctact	tgttcaattc	tattgctgag	actttccaga
67051	gcattttgca	tttctataag	ggtgtccaaa	gtttactgaa	gttttgactg
67101	ttttttattt	atgctatcta	tttccttgaa	tatttctccc	ttcacttctt
67151	gtatcatttt	ttggatttcc	ttaaatcggg	cttcacatat	ctctggtgct
67201	ccctgattag	cttaataatt	aacctcctca	atttcttttc	aggcaaatca
67231	gggatttctt	cttggtttgg	gtccattgct	ggggagctag	tgtgattttt
67301	tgggagttgt	aaagaacttt	gttttgtcat	attaacagaa	tcggtttctg
67351	gttcctttctt	acttgggtag	gctctgtcag	agggaaggtc	tagggctgaa
67401	ggctgttgtt	cagattcttt	tgtaccacag	ggtgttccct	tggtgtagta
67451	ctctccccct	gttcctatgg	atgtgacttc	ctgagagctg	agctgtagtg
67501	attgttatct	atcttgtgga	tctagccacc	caacaagtct	tccagactcc
67551	gggctggcac	tggggattgt	ctacagagtc	ctgtgatgtg	aaccatctgt
67601	gggtttctca	gccgtggatg	ctagcacagt	atttagggtg	tctcctaggt
67651	ccttcaggag	caatctgctt	cctgcagggg	gtctgtgggt	cctctctatt
67701	ttcgttttaa	aggcagactt	tgtaatagga	cacactagtg	ggcaatttat
67751	agttgtatac	tcataagcaa	actgtttaaa	ttatctgaat	ccaagtttcc
67801	tcatatgatc	acaagatgag	gtcccacaac	aggtcgtctg	caagctgagg
67851	agcaaggaag	ccactctgag	tcccaaaacc	ccaaaagtag	ggaagccgac
67901	agtgcagctt	tcagtctgtg	gtcaaagatc	caagagtccc	aaaattgaag
67951	aacttagagt	ccagtgttca	aggacaggag	gcatcccgga	tgggagaaag
68001	atgtaggctg	ggagactaag	ccagtcttgg	gaagtggctt	aaattaggtg
68051	atctgggatg	gtttttctgtg	gagctgacat	ttcagcaggt	acctgaatgc
68101	aaacctggaa	gtaacagaaa	ttcagaaaga	gaaaagcaag	ggcaaaggtc
68151	cttaggcaaa	aaaaaaaaaa	aaaaaagagc	ttggtgtgct	gatgaatagg
68201	aaggcaggag	gggcagaagc	agaatgagag	agagcatggt	agaagaccat
68251	atctgagaag	ttagctgagg	tcaatcatga	agaaccctgc	aggccatgga
68301	ggagctggga	ctttgttcta	agagatgtgg	ggaacgcctg	gagcagtctg
68351	atcataggag	aggcatgata	ttcaaagaca	ttccctggcc	tagctttagc
68401	atatctagtt	aaccttctct	ttactaatcc	tttacctttc	tttcattgta
68451	aattgagaaa	ttatagttgt	atatatttct	ggggtagaaa	gtgatgctat
68501	gatttacaga	cacaatgtgg	aatcattaca	tcgtgctaat	taacatatcc
68551	accacttcaa	atacatatca	atttttgtgg	tgtggctggg	tgcagtgact
68601	cactcctata	atcccagcat	tttgggaggc	caaggcaggg	ggatcatttg

FIGURE 1W

```
68651   aagtcaaaag ttcaaaacca gcctggccaa catggtgaaa ccctgtctct
68701   actagaaata caaaaattag ctgggtgtgg tggcggatgc ctgtaatccc
68751   agctactcaa gaggctgaaa caggagaatc acttgaacct gcgaggcagt
68801   ttgcggtaag ctgagaccgt gccactgcac tccagtctgg gtgacagagt
68851   gactcagtct cagaaaaaaa aaatgtggta agagaatttg aaatttagtc
68901   ttagtaattt tgaaatgcac aatacacatt actaactgta ttcaccacac
68951   tgtgcaatag atctcatata tatatatata tatatatata tatatatata
69001   tacacacaca catacacata ttgttcctgt ttaactgagg ctttgtgtcc
69051   tttgaccatc atctccccat tcccccaacc cccagcctct ggtaaccagc
69101   atactactct cttctaccat gggtttcatt gtttcagatt ccccatgtag
69151   tgaaaacatg cagtatttac ctttctgtgc ctggcttatt gcagatcatc
69201   tcattagatg cagaaacatc atttgatcaa attttatttc ataataaaaa
69251   tcctcaacaa attaggtaca gaaggaatgt acctcaacac aataaaaagc
69301   atatattata agccaataac taacattata ctccacagtg aaaaattgaa
69351   atcctttcct ctaagatcca gaacaaaata aggatgccca cttgagcaag
69401   atctagtgct gtgctggctt caggtctaac ccagtgcagt ctcagtgatg
69451   gtggccacaa ggctgcttgt gtcgcccctc accaagctcc aggcacctca
69501   gcacagagaa agagagactc gtttgtttgg gagaatgtaa ggaagagaac
69551   aagagttttc gcccagtaat ccagagaatt ctttcagatc ttattcaaga
69601   ccaccaaggt gatacctcta caagtctaca agaaccatag cattactggg
69651   cttggggtat ccccttaatgc agaaatgcct gcagtgacca aaaacttaga
69701   tcataatact gaagtccctt caaataccag gaaagccttc ccaaggagga
69751   tggctacaaa caagcccaga ttacaaagac tacaataaat acctaactct
69801   tcaatgccca gacactgaca aacaccacaa cctcaagatc atccaggaaa
69851   acatgagaca ctcaacataa cacagagaat gaattcagaa ttttatcaga
69901   taaatttaac aaataaattg aaataattaa aaagaatcaa gcagaaaatc
69951   tggaggtcaa aaatgcaact gacatactga agaatcatca gagtccctta
70001   atagcagaat tgatcaagca gaagaaagaa ctagtgagca tgaagacagg
70051   ctatttaaaa atacatggtc agcagagaca aaagataaaa gaataaaaaa
70101   gaaggaaatg cccaaaatat ctataaaata gcttcaaagg ggcaaatcta
70151   agttattggc cttaaaaagt agggagagag agagaaagtt tattcaaagg
70201   gataataaca gaacttccca aacctagaga aagatatcaa tattcaagta
70251   aaagaaggct atagaacacc aaacagattt aacctcaaag cattcactaa
70301   taaacttgca aaattcaagg ataaagaaaa gattttagaa gcagcaaaag
70351   aagagaaata aataacgtga aatggagctc caatacatct ggcagcagac
70401   ttttcagtgg aaaccttaca ggccaggaaa gagtggcatg gcatatttaa
70451   agtgctgaag ggaaaaaata ttttatcctt gaatagtata tctggcaaaa
70501   atagccttca tgaaggagaa ataaagactt tcccagacaa acaaaaactg
70551   aggcatttca tcaacaccag acctgtccta caagaaatgc taaagtgatt
70601   tctttagttt gaaagaaaaa aggcattaag gaaaaactaa aaaccatcta
70651   agggtagaaa actcactggt aatagtaagt acacagaaaa acagaatatt
70701   atagcaccat aattgtgcta attatttata ttttaagtag aaagacaaaa
70751   agatgaactt atcaaaaata accacaacaa cttttcaaga tatacacagc
70801   ataataagat aaagtagaaa caacaaaaag tttaaaagtg ggatgacaaa
70851   gttaaaatgt agcattttca ttaattttct ttttgtttat ttgtttatgc
70901   aatcggagtt aaattgtgat cagtttaaaa taatgggtta taaggtatta
70951   tttgcaagcc tcatagtaac ctaaaaatca aaaaagcata caatggatac
71001   acacaaaaaa ataaaaagca agaaactaaa tcataccacc agagaaaatc
71051   actttcaatg aaaggaagac aagaaggaaa gaaaaaagca agagaagacc
71101   acaaaacaac tagaaaacaa ataacaaaat ggcaggagta agtccttact
71151   tatccataat aacactgaat ataaatggat taaactctcc aatcaaaaga
71201   cacaggattg aatggattca atggattaaa attaaatttt aaaaagcaag
71251   acccaatgat ctgttgacta caagaaacat acttcatcta taaagactca
71301   catagattga aaataaaggg ataaaaaaag atatcccatg caaatggaaa
71351   ccgaaaaaga gcaggagtag ctacacttag atcagacaga ataggtttca
71401   agacaaaagc tatcaaaaga gacaaggaag gtcattatat aatgataaag
71451   gaatcaattc agcaagagga tataacaact ataaatatat atgcacccaa
71501   cactggagca cccagatata taaagcaaat attattagag caaaagagag
71551   agacatacce caagtcaata atagctggaa acgtcaacac ccaactttca
71601   gcattggaca gatcatccag acagaaaatc aacaaagaaa catcaaactt
71651   aatctgcaca atagaccaaa tggacctaat aaatatttat agaacatttc
71701   atccaacagc tgcagaatac tccacacact tctcctaaac acatggatta
71751   ttctcaagga tagatcagga taggccacat gttaggccac aaaacaagtc
```

FIGURE 1X

```
71801   ttaagacatt cagaaaattg aaataatatc aagcatcttc tctgaccaca
71851   attgaatgaa actaaaaatc agtaacaaga gaaaatttgg aaactataca
71901   aacacatgta aattaaacaa tatgctcctc aatgaccaat gggtcaatga
72951   agagattaag aagcaaactg aaaaatgtct tgaaacaaat gataatggaa
72001   acacaaccta taacaaaacc aatgggatgc agcaaaagga gtactaaaag
72051   ggaagtttat aactaaaagt gcttacatca gtaaagaaga aaaacttcaa
72101   ataaacaacc tattatgcaa cctacaagag caagagcaaa ccaaacccaa
72151   agttggtagg agaaaggaaa taaagatcag agcagaaata aatgaaattg
72201   aaacaaagaa aatacaaaag attaacaagg ccaggcactg tggctcacgc
72251   ctgtaatccc agcactttgg gaggctgagg caggcagatc atgaggtcag
72301   gagaccgata ccatcctggc taacatgatg aaaccctgtc tctactaaaa
72351   aatacaaaaa aaaaatagct gggcgtggtg gcaggcgcct gtagtcccag
72401   ctactcggga agctgaggca ggagaatggc gtgaacccgg gaggcggagc
72451   ttgcagtgag ccagatcac accactgcac tccagcctgg gcaacagagt
72501   gagactctgt ctcaaaaaag aaaaaaaaaa aagataaaca aaagaaaaag
72551   ttgtttttttg aaaagataaa caaaaatgac aaacttagcc agactaagaa
72601   aaaaggagag aagacccaaa taaataaaat cagagatgaa aaaggagaca
72651   ttaaaactga tactacagaa attcaaagga tcattagagg ctactgtgag
72701   aaactatata ccaataaact ggaaaaccta gaagaaatgg ataaattcct
72751   atatacatac aacctaccaa cattgaacca tgaagaaatc caaaacctga
72801   acagaccaat aacaagtaat gagattgaag ccataaaaaa aattatccca
72851   gcaaagaaaa acctgaaacc tgatggcttt actgttgaat tctaccaaac
72901   aatgaaagaa gaactaatac caatcctgct caaactattc caaaaagtag
72951   aggagaaaca aatacttcta aactcattct atgaggccag tgttatccta
73001   ataccaaaac cagacaaaaa atgcatttaa aaaagaaaac tacaggccac
73051   catccctaat gaacattgac ggaaaaatcc ttgacaaaat actagcaaac
73101   cgaattcaac aacacattaa aaagatcatc catcatgacc aagtgagatt
73151   tatctcaggg atgcaaggat ggttcctcct atatttagaa cacaaaaaag
73201   atgctcattt tcaccactgt tatttcaacat agtactgaaa gtcctagcta
73251   cagcaatcag agaagagaga aataaagagc atccaaattg ggaaggaaga
73301   agtcaagtta tgcttgtttg cagatgatat gatcttatat ttggaaaaac
73351   ctagagtccc catcaaaaaa ctattagaac tgataaacaa attcagtcaa
73401   gttgcagaat acaaaataaa atacaaaaat cagcagcatt tctatatgcc
73451   aactgcaaac aatctgaaaa agaaattgag aaaataatcc catttacaat
73501   agctacaaat aaaattaaat acctaggaat taaccagaga agtgaaagat
73551   ctctacaaag aaaactatga aacactgatg aaagatatta aagaggatac
73601   aaaaaaagga aagatatttc atgttcatgg attagaataa tcattactgt
73651   taaaacttcc atattcctca aagcaatcta caaattcaga gcaattccta
73701   acaaaaatac caatgacatt cttcacataa atggaaaaaa cagtgctaaa
73751   atttatatgg aaccagaaaa taccagaag agccaaagct atcctaagca
73801   aaaagagaaa aactggagaa atcacattac ctgacttcaa attatactac
73851   agagatatag taaccaaaac aaaatggtac tggcataaaa acatatactg
73901   accaatggga cagaagagag aaaccagaaa caaatccgta catccacagt
73951   gaactcattt tcgacaaaag taccaagaac atgcaacgag gaaaggacag
74001   tctcttcaat aaaaggtgct ggagaaactg gatatccata tgaagaagaa
74051   tgaaattaga cccctatccc ttgccatatg gaaaaaaatc aaatcaaaat
74201   gggattaaaa agttaaatct aagacctcaa tctatgaaac tactacaagc
74151   aaacatgagg gaaattctcc agggcaagga tttcttgagt aatatcccac
74201   aagcacagtc aaccaaggca aaaatgaaca aatgggatca catcacgtga
74251   aaaagcttct gcacagcaaa ggaaacaatc aacaaaatga agagacaacc
74301   cacagaatgg gagaaaatat ttgcaaatta tccatctgac aagagattaa
74351   taaccagaat atataaggag ctctcatgac tgtataagaa aaaataaaat
74401   aatccaattt taaaacgggc aaaaaatcta aatagatatt tctcaaaaga
74451   tgacattaca aacacaaac aggcatatga aaaggtgctc aatataatta
74501   atcatcagag atatgcaaat caaactgcaa tgagatatca tctcactcca
74551   gtaaatgaca ggcactaaca aatgctggca aggatttgga gacaggcaat
74601   aacaaatgct gacaaggatt tggagaaaag gacaggcaat aacaaattct
74651   ggcaaggatt tggagaaaaa ggaaccattg tacactgttg gtgggaatgt
74701   aaattagtat aatttagcca ctatggagaa gagcttggag gtttctcata
74751   aaactaaaaa tagagctacc atgtgatcca gcaatcccac tgctaggtat
74801   atttccaaaa gaaaggaaat cagtatatca aagagatatc tgcactctca
74851   tgtttattgc agcactatac acaatggcca agatttggaa gtaacccaag
74901   catccatcaa cagacagata aagaaaatgt ggcatatata cacaatggag
```

```
74951  tactattcag ccattaaaaa gaatgagaac ctgtcatttg cagcaacatg
75001  gatgcaagcg gagctcattt tgttgagtaa aataagccag gcacagaaag
75051  acaaacttca catggtctca tttatttgtg gaaactaaga attaacagtt
75101  aaggattaag aaaatgtggc acatatacac catggaatac tatgcagcca
75151  caaaacagga tgagttcatg tcctttgtag ggacatggat gaagctggaa
75201  accatcattc tcagcaaact atcgcaagga cagaaaatca aacaccacat
75251  gttctcactc ataggtggga attgaacaat gagaacactt ggacacagga
75301  tggggaacat cacatactgg ggcctgtcat ggggtggggg agagggagg
75351  gatagcatta ggagaaatac ctaatgtaga tgatgagtta atgggtgcag
75401  cacaccaaca tggcacatgt atacatatat aacaaacctg cacattgtgc
75451  acatgtaccc tagaacttaa agtataataa ttaaaaaaaa ttaacagtta
75501  aactcacaaa gatagagagt agaatgacgg gtaccagagt atgagaaggg
75551  tagtggagag agtgagcaga gagggaagcg gagatggtta atggacacca
75601  aaaaaaacca gaaagagtga ataacgtcta gtatttgaaa gtacaaaagt
75651  gtgactatag tcagtaataa tttaattgta cattttaaaa taattaagag
75701  tataattgga ttatttgtaa cacaaaggat aaatgcttga ggtgatggat
75751  acctctttta ccctgatatc atcattacat atcgcatgca agtatcaaaa
75801  tatcccacat aactcataaa tatatataac tactgtgtac ccacaaaaat
75851  taaaaattat taataaatta ttagtttgat ttaaaaaaaa caaggatgct
75901  cacttttgcc acttctattc aatatagtag tggaagtcca tgccagagca
75951  gttagacaag agaaagaaat aaaaggcatc caaataagaa aggaagaaag
76001  gaaatttttg ctgtttgctg acaacataat cttatatata gaaaacccta
76051  aagattccag aaaaaaactg ctagaactaa taaattcagt acagttacag
76101  gagacacaat caacaccaca aaaatcacta gcatttctat acactaacaa
76151  caaactttcc aaaaaagaaa tcaagagagc aatcccattt acagtagcta
76201  caaaaattaa aatacttagg aataaattta accaaggagc tgaaagacct
76251  gtacacagta gtctataaaa tattaaaaaa ataaattgaa gaagtcacta
76301  atccttttta aatccaccat gccccagtcc agctgaacaa ctcatacttt
76351  tcagaatcta ctctatgtgt tctcactgtc ctgcagctag ccacctcttt
76401  ctcctcccta gatcaccttc tttatcattt ctgcttctca aaatgttacc
76451  cctctttcaa agccaggta tgatgacatc tccctagtaa agctccctca
76501  acacctcaag cttataataa ctaatctctt ccttgaattc ccatagcagg
76551  ttatttgtac ctccattata atacctctct catcctgttt tgtattttaa
76601  ttattcatgt gtggcatgtt tctcttatta ggccataaat atcttaggac
76651  aagaactatg ccctcatctt tgttccacta caaatcttaa cacatacctt
76701  gcacacacca gaccttcagg aaatgcctgc taaggtaacg aagggacagc
76751  ctaaattaac ataaattatt atttgtgtac tgatccagtc ctaaatccat
76801  ggtgctatca tttctgtatc actgatggtt atccacttac ttaaataatc
76851  tttccttaaa tacacttaga aaagacggaa aactgtgtta taagggagga
76901  acaagtatgt aggttattcc tttccttaaa caaagagaag ttctgtcatg
76951  cgtcacggaa aattaaagca cagtaataaa aagcacgaac aagatttgtt
77001  gaataatgat ttagtggaaa cgttgcttgc ctcctgttca taggtcctaa
77051  ctttcctctc aagtacttaa gctgcacatt ctatttattt tgtttctagA
77101  TTACATTGAC AACTATTGGC TATGGAGACA AAACTCCCCT AACTTGGCTG   Exon 6(E)
77151  GGAAGATTGC TTTCTGCAGG CTTTGCACTC CTTGGCATTT CTTTCTTTGC
77201  ACTTCCTGCC gtgagtatct ttgcaccaat aaagcagttt aaattagatc
77251  ttagagactt attagagtga gctctcacaa attcgtatgc ttgggaacat
77301  atctatatca tttacaaata taattttcc gatataatgt tgacttttct
77351  aaatatatct acttggataa tttataaaat atggtcttcc cttggagaca
77401  cttaatctga gactttattt aatgtaggct catactttgt gacccaataa
77451  tcattcagat ggctcacttt ttaggcaaca tgctactaag acatttaaaa
77501  tatttgcaaa gatttaaagc tatattcttt taaaactgat ccttccaatt
77551  tggtttataa tgtgtgctac ttaagagaca gatgtgcaca atggagtatt
77601  tttctcttca gatccatttg agtgaaaagc atatgacctt aaagggtgtt
77651  aaacatgtca gatgatttat tcattgtgtc atcatcattg attttttaa
77701  tgagcagttt ctgtatctta tcagaataaa gggcacattt atctgccccc
77751  aagcttctga ttatttctc cttagtgaat gaagcctgcc tttctcatgc
77801  ttttattctc ctgtgtcttt aaaggcagct gttcaaaata ttacagtttg
77851  ccccatttc caagttcttg cttttgttcg ctccacctgg ggtagggaag
77901  gaggagccaa taaaaaggag ggttaacgcg gtgggagcag aagtgcttaa
77951  ggaaaataga tccagtcttg ctccagacac agctcaagct gtgccaacca
78001  gagaccccag agcacttctc caaagctctt ttaggtggta gggcttctcc
78051  tctgcctatt aataggtgca gagaacaccc ttgtccccacc agtgcccaac
```

FIGURE 1Z

78101 ttgagattca ccagatcgtt ctgccccaga acactcaaaa tccacagaaaa
78151 gagactgaaa aggccatgca catgcttggg tactagacct cagcttgaat
78201 acatctttgt cacatactaa ctatatgact gctttagttt actagggctg
78251 ccttaacaag taccacagac tgggtgactt aaacaataga aaggtattgt
78301 ctcacagttc ccaagactgg acgtccaaaa tcaaagcatt gagaaaccac
78351 gagagccatg agagaaagaa ctgttccagg cctctcttct tggcttatag
78401 atggctcttc ttcctgtgtc ttcacatcat ctgtgtccaa atttctactt
78451 cctagaagaa caccagtcat atttgattag ggtccatcct aatgacctcg
78501 ttttaacttg attacctctg taaggaccct attttcaaac aaggtcacat
78551 tctgaggtca tggggattag gacttcaaca tatgaatttt ggaaggacgc
78601 aattcagcct gaacagtgac cctgaataag tttctttttt aatagaatgg
78651 aggaagaatt attgagccca gagaaatttt gtgcggacca atgtaataat
78701 gtaagtcaag tgcttgtcat gaagagaact ctcaataaat gttacttccc
78751 tttgcctgta tgaatctaga aatacatgtt tcctggaaca aaacgatgaa
78801 atccaggaga attaaaaaaa aaaatcttac gtatccaagg caacttcatc
78851 tggcaatctc aacaattcag aacagagaag agattcactc aataatcaga
78901 ttccctacag gaaaataccт ttagaaacaa tacaacgcag tcttgggttt
78951 tttcccaaaa taatggcaca aaataattgc aacttttgtg tttatattta
79001 tcctgaggcc acatgtagag caacctctat gattcagtga aaaactatga
79051 acaaggaggt aggcaacctc tgggctgttg aaatagacaa caggctatgt
79101 tctgtcctca taggagagcc acttgagacc taattcataa cctagtcttc
79151 attcagagaa aatttctgata aactcaccta tatggtttca caattctttg
79201 aagattataa acaataaata tagaggaaga tgatagaaca aacactgcaa
79251 cagaaagaaa tggtaaaaga ctaacagcaa agaagggaaa aggaaatctg
79301 tgagtagcaa gcagacatca atgttcaaaa tgtgtatcct gtcagtaaaa
79351 ataaaattaa attaaaaggg aaaacaaaat gtatgaagat ctagggccaa
79401 ttagtgttag ggtcaacaaa cctctggaag ttggctgcac ccagcacagc
79451 aaaaaggcag tccccataat gaaactctaa actatcacag gggggttaaa
79501 tatgtcacta ggttaagtta aaggtcagag actaagcagt cattcttgga
79551 aatgtttcca ataaagtaag tacgaaattt ttatatgcaa attaaattaa
79601 cctatgttgg aaatctgaaa attttgcttt cacagaaaat tacatttctt
79651 aagaacccca agaaaagtaa cctctactaa ggatctttta ctgaaacttc
79701 acaatatttt ctgagtcctt atttattaaa tgaaagactg aatggtccat
79751 atataccttt agaaaaaaac aagattgcca gagattttat tatatcctgt
79801 gtatctgcca accaaaagag ttgtctgatt gaaatttagg aagacacatt
79851 gacattttgc tgagaaagct agaggtggat tgtgggctgc ccctatgtag
79901 ggttcctccc acccaggaca cctgagaacc aagaaagaaa agagcctttc
79951 tccatcttac cctcaaagca gaagggccat cctgcacatc acagagtcat
80001 acaagccacc catccaaagc gccactgtgg ggtcacttcc cctggtgccc
80051 gctccatctc tgggctaatg agctcacaga agaagcccca gctcccctgt
80101 gttaccctga tatgcaggtc tttctccttt ttagagtgct cccttgtctt
80151 ctgctagata ttcctgctaa gagtattttc attgatgaag aaattgagtt
80201 ttatagagac tgaattcctt gagacctcca gctagtaaat tcagtgcaag
80251 aactagtgct gtttgactca agatattaac cattccatta aaaatattgg
80301 ccactgtaat ccttaacaat attaactaaa tgtaattatt gcatataata
80351 acatgttaaa aacogtttaa aaaaacaggg catcttgctg ggcgtggtga
80401 ttcacgcctg taatcccagc actttgggaa gccgaggcgg tcggatcaca
80451 aggtgaggag atcgagacca tcctgcctaa catggtgaaa ccatgtatct
80501 actaaaaaat acaaaaaatc agccaggcat ggtggcgggc acctgtaatc
80551 ccagctactc gggaggctga ggcaggagaa tgatgtaaac ccaggaggcg
80601 gaacttgcag tgagccgaga tcgctccact gcactccagc ctgggcaaca
80651 gagcaagact ccgtctcaaa aaaaataaaa aataaaaaaa ataggatgtc
80701 tttcagcatt gcctatttgc tatgtgtggg ttacaaatta ggttcattta
80751 atccagaaga taatgaaggg taaatttctt tacatttatt ggtgtcagta
80801 tttgaaggga tgacatatat gttcaaagct taagccatgt tttatgtgtg
80851 tatatacaaa tataatagac cttattttca cagacttctg tttaggtgca
80901 ccaagctgtg tactaagaga gaggtggaaa aaaattggaa aggagccatg
80951 atgagacaat aagcagacct ggtttaataa ctgctgtaat gtacagtctg
81001 gcgcaagaaa tacgtagtga acatttacca ttcactaata tatgttaccg
81051 agcaatgcca atgtgatttt cagcacattt tagattgttt ggcagatgat
81101 aaatttgtgc tatgtagggc ctgtctttat tttccaaagg ggattaaact
81151 ccgaacctca catccacatc ataagtgctc aaaatggtag ctagtgctgt
81201 taattcaatg tctgcaaaat ctaaattatg ctccatacaa gtggattata

FIGURE 1AA

```
81251  cacatatatg cacataaatg catgtatata tactacatat tataaatata
81301  tgccagaaat tttggtattt catattctct tacatgtcta cactttatga
81351  aaagtagtat taaagggaaa ataaagaaat ctttcctaaa tgatcttaca
81401  cagcagaaaa aaattagaag ttacaaatga cttaagttgt tctggattta
81451  gaaatggagg ggcattttta taacacctaa atggagggaa atgttgttta
81501  aatctataaa ccagatcaca gagaccaggt ttttataaag cttagtttgt
81551  acaatcacaa cctgtatgag atagagatct tagacagcgt aagacagtca
81601  ctgaaaagga gagatggaaa acagaacctc tgatgtaatt tctaatttca
81651  tagtacagtc atttatacta attaataatg gagtagatca ttgctcacga
81701  gtagcaaata gtattatcag accactgcat atttaaaaca tgattgcatt
81751  acttattgtc tggttattgt cactgatgta ctcagaagtg tggaatctca
81801  agataagaag gaaggttaaa ggttatctag agcccaaaaa tatctcagcc
81851  aagttgttat tcagttgaga cttaacacct tctagaaatg aaaaacccac
81901  cacctctcca gacagcctat agcatctttg aaccatcttt gagctactct
81951  aaaaataaaa agaaaagaaa agcaaccatt ccttacctgt agcaaatact
82001  gacttagtgc ttataaaatg tccatctcta acgaaagggt tagactcctt
82051  gaagtttaat aaaaaactaa taacttatag ctagcaagta aaatccacag
82101  acttgaaagc agcagagctc ccagccccat gctaataaac tcaagagtta
82151  aagacaaagc ccagagactg aatttagcaa gctccaaaag ccaacccaag
82201  gctgagacaa agcatcttgt ttttacaaat gttagtagac cagagcaaat
82251  tgaaaagagt gggggacatc aaagaaccag aattttggca gatcaagatg
82301  ataagcagaa gaaaagcaaa ctggcccaaa actaatgtaa acctagaagg
82351  gaatactaat cttactaatc ccaaaaactg aataggtgag ccaaaataaa
82401  aaaggcaagg aatggtaaaa gtgtgaatta aaatgggaat gtgctttgca
82451  atgatccacg ttcttgtctc tagtgtacaa atgggcaaaa tagaaaacct
82501  tctactctgt atcttcaaaa ctgagtatcc ctgctctcca ttttactttt
82551  cttttagtag gtgtacagtt ataacattat aaagaactac agctgggaca
82601  gattttatac agtcctctct cctccatttc atgaatagag aatctaactt
82651  tcagagtctc atcaaagtgc tagaagtatt cccatgttca cagcagtgag
82701  actttaactc cctcagattt aaaatccagc tctgtcccaa gttgaaattc
82751  atgttctcta cattccatca ctggatgaga ccattcaatc taacttaggc
82801  aaaaagaaat gtcacagaga aggccacaca cacaaaaaaa aattttattg
82851  tgattttatt tataatcatg gtgcctatgc tataccacaa aagataataa
82901  atgacaatgc ctaattgact tactaaagaa cagaagttgt atctcctggc
82951  agtattgccc aacaatttgc cattggctat tggtattata atggagataa
83001  atactgctta ttttaataag taacatgttt atggacaggt tacataccgt
83051  ttgtcttctc tcagactcat tttagtgact ttttaatatt tgtattattt
83101  aacagtgctt ttgaaatttt tgagtgccat ttttgtattt tgttccagGG
83151  CATTCTTGGC TCAGGTTTTG CATTAAAAGT ACAAGAACAA CACCTCCAGA  Exon 7(C)
83201  AACACTTTGA GAAAAGAAGG AACCCAGCTG CCAACCTCAT TCAGgtaaat
83251  gtcaatgtaa taggtagatg gcaacatttg tgtccatagt gcttgatggg
83301  tcattttcca atctctgtgc ttcattgctt ggtagaacta ctgctttgtt
83351  ccttttcata aaatgaagtc agaacttaat gtacagtctt ggatttggac
83401  agtcttggat ttgttcctcc tctcccaaac tgaaacacat gtatttttag
83451  caaatggtcc atgcattgtt cagactaagt aaccatgtca gcaaggccat
83501  gcaaaggtta gcagttgtgt ggctcgtgga attatctaat atgtcttatg
83551  aattacttga tgaaacgtaa ttgatcatta agtgatggag cagaacaggg
83601  cattgttccc tgcattccaa ttactttctc cagccagatg tatgttgctg
83651  ttttaaagaa caacatattt gtttagaatg tcaaggttta atacctgtga
83701  aattgctttt agtgccattt agggcagtta gcggaaatag ctatcctatt
83751  ttgagagctg atgggactat ggaatacatc agtgtttgag aatattaaac
83801  aataagtata taatttgaag ctagctccta atacataggt tgttatttag
83851  tatttcattt tcttttcact aactcaggat tagcttcagc actaaaagga
83901  atgcttctcc ttttgccatc catatatttt ccatcctaga tccaggttaa
83951  gaatcacaaa atatattttt tgttagattc ataatgtaga gttgacattt
84001  agttatggac aaaataattc tacaatctaa agtttctccc ctcctgctag
84051  ggaagtggaa gctaccgaat ttctaaactg gagggtcttg aagtggtgct
84101  ccaaggccct aggaaacttg ccttaaagct gcagtaacgg gcacactgtt
84151  ttgttgctgt tgttgttttg ttttattttt tgtttgtttt gttttttttt
84201  ttttgagaca gagtcgcgct ttgtcgccca ggctggagtg cagtggcgcg
84251  atctcggctc actgcaagct ccgcctcccg ggttcacgcc attctcctgc
84301  ctcagcctcc cgagtagctg ggactacagg cacccgccac cgcgcccggc
84351  taattttttg tatttttagt agagacaggg tttcaccgtg ttagccagga
```

FIGURE 14B

84401	tggtctccat	ctctcaacct	cgtgatccgc	ccacctcggt	ctcccaaagt
84451	gctgggatta	caggcatgag	ccacggctcc	cggccacaag	cacactgttt
84501	taatttagat	tgtaggtttg	ggtgggtggg	ttggtgggag	ataaccacca
84551	caacccctac	ctttagtgtt	gatatgtgac	tgtgatatat	gcagtgcctc
84601	ccacagacat	ggagctgggg	aaagaagggg	gcagtatggt	tcagttatat
84651	catgaaggag	atctgtttat	atctaatcat	taaatgagga	tattaatttt
84701	taaatcaagc	tattctctaa	ctgttgacaa	gaaagtagac	catcaggcat
84751	gacttccagt	gcaaatcact	gagaatctct	atttttttac	attatttttt
84801	acaatttttt	ttttttacat	attctttaca	ggttttaaaa	ggtcactaaa
84851	gagaaagtaa	actctatttt	cttatatgaa	gttggagttt	aagatctgat
84901	gccaaacaat	aatcagcaga	atgaaaagag	gagtcacaca	ctttaggaca
84951	cacgcaaaat	accccaaggt	ccagaattca	taggctttca	tcctttagca
85001	ctccttaact	ggttacacat	gttccaatac	ttctaataag	tttttctctt
85051	tactgttctt	atcctttaat	tttccttcac	tctagaacaa	cgttttccaa
85101	cctgtgagtg	cagaagttat	tgcatgggtt	cctttcatcc	gtctgagcac
85151	caagctctgt	ctacatatgg	aaccaataat	acattttaca	caataaaacc
85201	tcttggaata	tcagctgctt	tgttagaaag	tgagctcttt	gaggaatttc
85251	tcatgcacat	atcaattgtg	atgatacaaa	gctgtgccgc	tcaatacagt
85301	aaccactagc	tacatgtagc	tttttacatt	taaattaatt	aaaattaaaa
85351	accaagtttg	ccaatggcac	tagccacttc	tcaagtgttc	aatagctaca
85401	ggtggctatc	ggctgccata	ccatacaaga	gaaatataga	gaataactgc
85451	aggaaatctc	ctgatctaac	ttgtcattat	tgactactaa	actgtgcaac
85501	aataatttcc	aattgaactt	gaaaataaat	tgctatttct	acagcaaatc
85551	attggagcag	aggcatttat	atgtctacag	tcaaaatgag	gcaaggcctc
85601	cctcacaggt	aaccctgtgg	aggacaggct	aattgaacag	ttttacttgg
85651	aggcctagaa	ttttatttta	tggaactggg	ttatgtaaca	tatattgtga
85701	tcagtaattg	aacttgtaca	aatgcaggta	acaatgaagt	aaaatcgtga
85751	gtttttattt	tacttaaaac	tccaacttaa	atgttgttct	taacaaaaat
85801	aatgcaaaat	ggaatgcttg	aagcattcaa	gagtactttt	aaaatctaat
85851	catagtttca	ttaatcaaag	tagaatctac	taattttaaa	agcaagtgct
85901	ccttcattta	aatgcaatta	atttattaca	cacagaaata	ataatataat
85951	tattaatttg	ttcattgttc	ttccttgcta	tagtctttag	acagaattca
86001	aggctttaag	ccttgattat	atattataga	aatttatatt	tcaggatgta
86051	atagattgaa	aagcaaactt	catttaatca	tcctttcacc	ttcttaccca
86101	ataaacctga	cttggtctgc	tgaacacaca	aaccatcaag	cccaaaagcg
86151	tctcatttat	tttaggccag	agtcactgtc	ttcttaaaag	ggcaactgag
86201	atgcccaaat	tgcttcatca	tttggttggt	gagagaacta	aattaaccaa
86251	catttcaggg	ttttaggaaa	aaaatttaaa	accccagaag	cttgcagcaa
86301	atttagctgt	gtcaatatct	ttgcatgatt	cttttaaatt	tgctttttcat
86351	ttcaagctgg	agcagtctgg	aaaaagaaat	tagctctcag	taatgttttg
86401	aataccctgcc	caaatgtcac	aactttttatt	aataatgctt	aagactcatg
86451	aagtgctttt	tagtttgcag	ggtgcttcta	atacattatg	ttacttgatc
86501	ctcgagacaa	gcctaggagg	agctaggact	caaatccctg	ctgtctgaat
86551	ctgaatccat	taccccttttc	aaaaagcagc	atttacatcc	tcataaatat
86601	atgctttatt	agaaacagaa	acagggaatt	aagtaaaagt	ttgtgaaata
86651	aatgttggta	gggatagatt	agaagatgtt	gctttgatgc	caactgaccc
86701	aaaagaaaaa	tatatatatt	tgtcttgaaa	ctttggcttc	ccctagtaaa
86751	atgacttagt	ctccacccaa	ttaccctaaa	gcgaagccac	tagtcattaa
86801	gctcaagcca	cttatataga	gattttacat	ctttttagtg	ctccagtcat
86851	aaataaaaac	agtgccaggt	gtggtgactc	atgcccgtaa	tcccagcatt
86901	ttgagagggc	aaggtgggag	gattgcttga	gttcaagatc	agtctgggca
86951	atatagtgag	accacatttc	tttaataaat	aaataaataa	gaacagactc
87001	agaaaaaaaa	atcttagatg	tgaaaaacat	gaaggcagga	aaaaaaacag
87051	aaggtaagat	aaagttgtga	aaatttccct	gaaactagaa	taaacagaga
87101	ttgaaaataa	agcaaaaaag	ataagaaaca	tgaagtgtcc	atccaggcat
87151	tccaatatcc	agctaataaa	gatgtctcag	ctcaagtgca	gggaaactaa
87201	gaggaagatt	ttatcaaaga	aatacaacat	tatgattctc	cagaacagga
87251	ggacaggagt	ggccacagta	gaagagctca	ccaagtgtcc	agcactgtga
87301	accaaaaact	tcacaccaag	attatcacag	taaaatatca	gaaaacttac
87351	caaaagggga	tcctaaatgc	tttctgagca	ggacagagcc	aaaggaacaa
87401	gaataaggat	gacataggat	ttctcattag	taatccaaaa	attagaagac
87451	aatgaaacaa	tactttcgaa	attatagaaa	ttattttcaa	cctagaacgc
87501	tatatccagc	caaaccacca	tcaagtgtga	gagcagcacc	aaggcacttt

FIGURE 1AC

```
87551  taggcatgca agatctcaaa aattaatcca ccatttacct ttactcaaga
87601  aactttgtaa atagaacttc tcttccacaa caaggggata agccaagaga
87651  gaaagagaca tggagtcaag aaaacaagag attccgcaca ggaaagagca
87701  aaggggattt ctatgataat agggaaggga agtcccaaga caacagctat
87751  gcaggccttg agaacagaat gagaaggagg ctgagagctc caggagaaag
87801  atcttcaagg aagcgaaaga atggagttct cagatttcat gatgcatttg
87851  accagaggaa ttttatagtt ctgttggaaa gatctggaat gtaatcataa
87901  caggtacata taggcaaatc aagaaattaa aataggggcaa ttataactcc
87951  aaaaaaacca aaaacttgta taagaaagaa agagcagcca tagtacatca
88001  cattgctgaa ctgggaacag cagttacatt gtcataataa tattaaatag
88051  taacttagct aagaattgtg atattaaaat gttgatagga tgaaaggagg
88101  ggaagagggc atgtaagtgg gcaatatcat tatcgttcag gataggaagt
88151  taattgataa tgtctaaaat tgaaaaatca agaaatataa ctataagcat
88201  aatccttaaa aataagcatt cttggctgga cgcaagtggc tcatgcctgt
88251  aacccccgca ctttgagagg ctaaggtggg aggatcactt gaggccagga
88301  gttcaagacc aacctgtgca acatagcgag accccacctc tacaaaaaaa
88351  ttttaaaaag tcaagtgcaa tggcacacac ctgtagtcct cacacacctg
88401  tagctactca ggaggctgaa gccagaggat tggttgagcc tgggagtttg
88451  aagctgctgt gagctataat tgtaccactg cactccagcc tgggtgatag
88501  agtatgaccc tgtctcaaaa ataataataa taataaataa ggattcttaa
88551  aaatagaagc aacaactata agaattgaag gggttgcctc tgaggaacag
88601  aaagtagtgt gaagaaagat gtggaaaggg attgctggtt catagcctaa
88651  aactttcagg actttcacat tttaaactct gtaccttgaa aaaataagct
88701  ctgtgttcat tattcctttg gatggtcagc tgaaacgttc taaaccattt
88751  ccagtaagga tcaaacatgc cataatggta atacttgcaa gacaaacaaa
88801  atactcccaa aaaaactgaa ttatactggc cttgtactta ttgagcaaag
88851  tccaaatctc tttgactgcc tagagcacca gcatcacctg ataaatggca
88901  aagttggctc tcattttgct tcttgttgat ttgtcctttg aattgtatac
88951  accatgtaaa ttaaccatag gaaatccctc taagtgttat ttttctcttg
89001  ccaactactg tgtgattttg gctttaaata taggaacatc agctactgga
89051  tcacagggat gtgggttcaa agttcagcta ctagaaacaa tttgctaaga
89101  gagacctaag aacaaaataa agttattaga gtgtaacggg catagagttc
89151  cactttccac cttcattttt actgttaact aatatcagcc atgtgacaga
89201  tgccacctgc accttccata cctctcattt aaaaggcatt tttgggagat
89251  gagtaatgaa gggaacaaga gcttagctgt tgggatcaat ctgagagaaa
89301  aatagcaaga catcaggtct cattgtaaag aaaatcttta attttctcag
89351  agtggcctct tttgcccccca gttctttata acattcacag gcaatgcctt
89401  ggtcccattc ttttgttgtt ctgttgtttt ggatttttttc actggtatct
89451  aataatgtgc agacctgcca tatgcttcta gttctacagg agtcttgctt
89501  tcaatgtatc aaaaatcata tatgtgtgac atcttctatg gaaattgttt
89551  aattaaggca gccgtctgtg tcatcacaac attagaggat ctctgggcat
89601  cactactaca gaagaagctg caatcctaaa tccatgtgtt ttccttaatt
89651  atttctaaatc actctataaa ttgtgcaggt ataatatttg caaagattaa
89701  catttcaaga tgatgcaaca atagttgcat tatataagat gtcaagatac
89751  ttagcacaaa tttccacaga tttgtagatt aaatcagcat gagccatgta
89801  atgaaggcaa ggaactttgg ttcaatcatt taaaccttcc tcaaaaatat
89851  aaaaagtccc tcagtttcta ccactatatt tttctagttt ttttatgtca
89901  ctttcctgaaa tttcattgaa gtacaatgtg catgcagaaa agagcacata
89951  tcttaggaga actgagcaca cctgcataac cagcactcag ataaacagag
90001  caggacctcc tgtgtacccc ttcgcaatca ctatcccata aggataacca
90051  ctgtgctacc ttctaacagc gtagaatagt tttccctggt ttttgtacat
90101  tatggaaatg tactccttgg tgtcttcttt ttctcactca acgttattca
90151  catgaagttc atcgatgttg ttgtgtgtag ctatatgtac tattgccata
90201  tagtattgta ctatgtaaat ggtgtcacaa attttctgtt tattctactg
90251  tttctgggta ttttggaatt tccagcttta gtttattaga aaccaacata
90301  tagtacatat cttttaatga acatatataa gcatatattt tgaaaatata
90351  cctaggagtg tgtagttgta tcataggata cttaaatgtt cagctttcgt
90401  agaaacttcc agtttttcccca agtagttgtg tgaattttta acttttattt
90451  agcatacatt tattcaatga tattctcagg aaaaggaata ttgttagatc
90501  acattttctt cattatggat ttcacaatca tgactgatgt gttatgtact
90551  agggatgtgg cccatttaaa tgaattggtc tgccaggcat ggtggctcat
90601  gcctgtaatc ccagcacttt gggaggccga ggtggcagat cacctgaggt
90651  gaggagttca agattagcct ggccaacata gtgaaaccct gtctctacta
```

FIGURE 1AD

```
90701  aaaatacaaa aattagctgg atgtggtggc gcgtgtctgt agtcccagct
90751  actcaggagg ctgaggcacg agcatcgctt gaacccagaa ggcagaggtg
90801  gcagacagcc aagattgtgc cactgcactc cagcctgggg gacagaggga
90851  gaccctgtct caaataaata aataataaat aaataggttt gtcacataaa
90901  ataaaatgtt ttgattaatc tactataata aaaaagtttt ctctgagggg
90951  actggagtaa atacctggcc attagagatg tttgcagact cattaaaaag
91001  aaagaaattt acccaaatct atatgggaaa gtaaggtcgg gcaatctctc
91051  aaatgagcag ttcagatgga agcttttcca ataacagtct tcaagcagtc
91101  agcaagtctc cgtggaggga ttctatgact gacagccagg caatctgaga
91151  tattgtctca actccaccaa ctttgtataa acctcttcat ttatctgagc
91201  cctttttttc tcacctacaa aaaaggaatc ttaattcaca ctttgatggt
91251  gaggatcaca taaaatact ttgtcttatg tatgccaggt gtaattatat
91301  gaaatggaga gagttgatgt tttacatcaa agagctataa acatattctt
91351  agatcatggc ataaatccgt aggtgttttg cagctataca cctagagagt
91401  acattttccc catcttgttt tagctctgct tcttgatatc actatcttca
91451  ttttttagcat tagaagtatt acatagttca aggatttcat taattcaatc
91501  actagcatac cctggtgttc attagttaac tagttagctt actagttgca
91551  taatggattt tcattagtcc tttgcttctc ccttatcaaa tattgattaa
91601  agatcaatct ctagaatgta tgctcatgct caagtcgctc acctaactac
91651  tatcttggat attagcattt aaccagtcaa tcattacttt ttgttttgga
91701  taatatagta tcttttccctt accaattcaa aaattacatt atattgcact
91751  ttttgggcct tttgcttctt ggtatgttgt tttgaaaaga agctctggcc
91801  aggcacagtg gttcatacct gtaatcccag cactttggga ggccaaggca
91851  ggcggatcac ttgaggtcag gaatttgaga ccagcctggc cagcatggtg
91901  aaactccatc tctactaaaa gtacaaaaaa aaaaaaaaat agccaggcat
91951  ggtggtgggc acctgtagtc ccagctactc tagaggctga ggcacaagaa
92001  tcacttgaac ccagaaggca gagattgcaa tgagctgaga tcgcaccact
92051  gcactccagc ctgggcaaca gagtgagagt ccatctcaaa ataaataaat
92101  aataaaataa aataaaataa aagaagttct gatgtggtgc aatatgttta
92151  acagccagct gaaaatgcca aagtagcctt cttcctcctc tgggtattta
92201  tcagggctaa gtataagagg caaaagattc ttcatgtgta gtaacttaat
92251  catttctctt tttattttat tctaaatcct gctctctttt ttcttttttca
92301  tgtccccatc tatgccacat gcagTGTGTT TGGCGTAGTT ACGCAGCTGA
92351  TGAGAAATCT GTTTCCATTG CAACCTGGAA GCCACACTTG AAGGCCTTGC
92401  ACACCTGCAG CCCTACCAAg taggtatcag tgtgacagct gccactgtag
92451  ttgagtcttt tcaagtctgt taaacaaacc atacccacac acacaaaaaa
92501  aggtgttaat gtttggcttc tcttattctc tgttgctcct agagagattc
92551  aaacctattt agtagcagtt ctggcacaaa actaaatgga atcagtatca
92601  ttcctcacaa tccacagact ggggttaaag attaaaataa tgtaaatttt
92651  atagagattt atttttacta tttcatgctt actttctaat gtctcatttc
92701  gtaaagccca ccagcatcct aaaggtaagc accacagttc ttgaaaaaca
92751  aggattattt attttgcacc catcgcctga tcccaagaga tgagtgctta
92801  gagagtaatc catctttgta cgtttagatc tctcaaagcc atttctcatc
92851  tggatcctct ctggatggtc ctcaagcttt tacttgcaga tcaaactcac
92901  atcagtggca aaaaaagaga aaaatagggag tcctaatagg attatagttt
92951  acaatgaggc aatgggaccc agcggattaa aatttggaat ttgcattcac
93001  aattttaaag taagactact tttcttcaca tttcattggc caaagtaaat
93051  cactcagcca tgcctaaatt caaagaaaat ggggaagtac aattttacct
93101  tttaccatgt gcctagaagc aggcaagaac caaggacatt atggacagtc
93151  ctaatgatta ccacagagat ctgtaattaa aaaaaaaaaa aagggcttag
93201  tctttggagtc ttggaaacct ggactccagt tcaactatca cagaaaatgt
93251  taaatcatat tcaccaccta attaaagaag tcctcattga aataccgaag
93301  cagtaagtca tgagaaaggc tttctgtgag tcacccagct tgattagcgt
93351  agtcagttcc tcaggttgtt caaaagttat taaattgctc atccgacatt
93401  tgagagcacc agctgctttt cttcatagcc caacaaaacc ttaatcctag
93451  tggcttcatg ggattcggga cacctaacta ctgtgactca caaaaaacca
93501  cctgttcgta ctgatcttgg gagatatcag ctgaggaaac ctccatgaca
93551  ttccctggca gtaccgtctt aatggaggtt tgtgatgcag cagaatgcat
93601  accattggga agcaccagat ccatcattaa ctacattact tccctgttct
93651  gcccctggcc tcagttttcc cacccacaaa gagaaggaca agagttgggc
93701  aagatgattc ctaagctcta atgggaaatg cctcctggtg ggtggtatct
93751  aaaattcttg tcagcaccta ggacagagat attcatagca ctccagggat
93801  ttcagagagg atggaacctt agcatggata gaagcacgga tgctgttgaa
```

Exon 8

FIGURE 1AE

93851 tgcatgtttg gattaaaatc ctcttttcat ttagatcttg aagtttagct
93901 gaacttttta tggagtttaa gacccttca acattttgat atcaaaaaac
93951 cgaaaataga acctaactcc tgtgccattt attccttggg agtatgaacc
94001 aaaaataaaa attatataga aattgtattt cttgtcttca tgaagtttgc
94051 taggtaaatg taaaaaggga atctgagtag gaaaactgat agagaattct
94101 caagtgacag aggagagtgg tctattatca tatgtgatta tttggcttcc
94151 cacttactgc agtttttgga ttaaaagtca ttaaaagcct ggaaaaactg
94201 tttaataatg agtcaaattc ccccagtaaa tcaactatta ttttattcac
94251 ataagttctt tctactcctc tgatattttc cctgtcttaa gtgggggtgg
94301 aggtggagga ggatttatgc aaacacctgt gttcctcatg tcctactgtg
94351 cctttccctc actttccttt tcctgcaaac tcatgaacca tggggctcag
94401 ctccattgaa tgaagaacag ttatttgtcc agaatgacac agcagtcact
94451 ggtaaagttc atgggaaact agatgtccta acatctctcc cctttccagtg
94501 atgcttcatt gcttcaaaat gcagaggttc ttaatccttg ttgatgtttt
94551 ttgttaaacc attgagaatg tgatggaaat tatggggtct ttcccaagaa
94601 agataatcaa tgcacgagaa aatcaatact ttgcctacaa ttttaatgta
94651 ttcacagagt ccctgaagcc aagttcaaac ttttgtttta caaagcaaac
94701 ttgctttaat caagtgacaa taattttcag tgacttagag ggatcttttt
94751 acatttaagt ggcttaccga atggagagtg ttgtagtaag aaacagacta
94801 caattactat tttatttaca ttgtgtattt tcctttagca ttcagcctaa
94851 gaacttctga tgggaaagat catttattca gtcatgtatg cattcaacaa
94901 ttactcattg agcacctatg atgtgcaagg catagttcta ggcactgaga
94951 atgaagcagt tggagtaaaa aaaaaaaaaa agttagaatc tctggccttg
95001 ggaagtatgt attcaaggga tgttgggata gacaatataa ataaataaat
95051 ataggatatg ttagatggca ttaagtgcta aggagaaaag taaaataaag
95101 aaggaattta gggagcatca gaggctataa tttcaaatag gtggccaggg
95151 ggaagatcaa tttatcaaca atatcatcat catcatcatc aatgttactg
95201 ttatcattaa aaaacaccag ccccatgctc ttgttcccca gttttaaaga
95251 catagtggga tgctttgatt ccactaaaca ggatgaaaga gaggtctaag
95301 aaacagctgt gcagggcaga gagaaatggg aggagggaca ctcaaacctg
95351 ccagggatac aaccagcagt tccttactct ctcttttcag gtctggtttg
95401 tctcttacat acacttttaga ggtcttagca attctatttc aaagttttat
95451 tttaataaca gaaggatgta tagaagcaag tactttttctt gatttctcc
95501 tcaaagagag tgaagctgca aagggcaaaa cacaggtaaa tatgccattt
95551 agggaatgag tcagaaattc tatgaggcta tggggaatta tcaagctcca
95601 aaaacacctt gtggtacctt aagaagtggg gatttggaga ttatctaacc
95651 taaagccttt gatttactca taagaaaacc aaaacctgca agcaaataag
95701 gtgcctgccc aaaggcacac agctcgtttg caaagagtac agaccctaca
95751 ccatggtgct tagacctaca tttgctaaaa tgagttatta caaatgccac
95801 ccaacagtat aggctaaaag agttttggta aatattctat gtaccttatt
95851 tactccaagg aaatttagat tttatacgat acaaaaaaaa atctgcctca
95901 gcaagtgact gagatacaat tcattaatga atccaggttt agaaaccaaa
95951 gtctgccaga tgcacagaga acagttatgt tgtaactagc aacattctaa
96001 gagcccttgc taattctggt tagatcagaa ccactttttc ttagccatgg
96051 atagctttgg ctaatgaaaa gtctattgtt ttttattcta tgtgggcagt
96101 cttggctttg ccaagtaaat gttgtgctat ctctggtctg tatcacaaag
96151 aatatatgtt agcaagttga gtacatttat tataaagaac actgcttttg
96201 tggatcttgc atgaaaagag cttacttaagg tatttgattc cccaatctcc
96251 aatttggcca ttatcaagtg ctataaatat attcactggt ttatcatcat
96301 ttctcttctg cctgcacgca cctgaagGAA AGAACAAGGG GAAGCATCAA Exon 9
96351 GCAGgtttgt gatttctctc ttgctacatg tttgtttaca aatctgatac
96401 ctaccaggtg ttttaaaagt gtctcatgtg agtaaaatcg atcaacaaat
96451 acaagatgat taaaagtgac ctttcacaag attgcctgca aagattgcta
96501 ttttattgat atttcgcccc ttagtatcaa agtgtctttc cctaactcac
96551 tccctgcttt ttcaaaatct gcagggcatg gaacatttgg aggtgggga
96601 ggagggaac tgatcttgga ttagtccttg ctgttgtttt cccagacaga
96651 agtcttatca aagtatttaa atatggtaat ctagagaatg aaagaaagaa
96701 attttttttc tgaatgtaaa aagtccaggc agcagtctag gatacactcc
96751 cctttcactag ggtcctttctt ttggagtgat atatatatat atatatatat
96801 atatatatat atatatatat atatatatat atacacacat atatatatca
96851 tatacatata cacatacata cattatatgt atatgtatat atacctatac
96901 atataatctt tttttttttgg caagatgaaa ccacctctct gtgacatctc
96951 cagatctcca gcccactgag tgctgaggtc tactcaagtg actcaaagag

FIGURE 1AF

```
97001  ccccatcccc atcttttagg aagaagacaa ccctccccaaa aattccccaa
97051  ataatttatt atcagcttcc catgacttag atggaatgcg tcgtcagatt
97101  acagcagaga attaaaccta gagggaatac gaggtgaaag aaaaatttct
97151  tgatctgtgt taatgagtac caggaagtgc ctagatttga gagcaaagcc
97201  ctgaaaaaca gagccaggtg gaactcagta ttaatgatgt gaagagtggc
97251  agaggcagaa ccagcaagga gaatcccagg tgcctggaaa ggaagaagag
97301  atacattttt tttcctatca ttgtcactgt gtttccataa agaaatgaag
97351  gcatccacct acccagagtt ggtccctaag tggaggccag tgtgggccca
97401  gggattgttc ttttagctta gtactattat aataattata ttaataataa
97451  tatatttatg caatactgaa gccagttttg aaagttcact tggtgtatta
97501  aggctctgga ttatccattt ttgcactatg tttatatgta aagataaaca
97551  aatgaaaaca taaatgcatt cgtctatgat gggagatagg cacgatagga
97601  tatacaacat caggcacatc ttctgcgtag gtaacctacc caagggatgg
97651  cattaaagtt ctttctctta tttggtagca tagagttaga gccaagggca
97701  ttggatattc cttggagata tttccagaaa aaagtcattc ttccccacct
97751  aagaaacgtt tttgaccaaa gagaggttct agtcattaga ttcggaatag
97801  tctttgccta gacactggaa gagacaagct gaccaattct agacttttag
97851  tccatttttct agattccata cagagctcac catccttctg ttgtgacaat
97901  tttacttgaa aaaagttaca caaaataaat catagccatt ttaaggtagc
97951  ttatagttgc tttggtgata ttttaaaagc tttcattgtc tcaggagctt
98001  tccatttact aattatctca aagggtgatc tgcctccaaa tccaaaggac
98051  agagaccatc tttggcacaa attccagagc tacctgagag tgcgatcacc
98101  catcttagtt tcatcctcca aaacggagct gttaacacct aaaagagaag
98151  tttgtaaatg acatggaggt gcttgaataa gtgtaaactc tatggcaatc
98201  ctgaaggagg ggacaccttg ggctggcaca atgatattgt actgtttta
98251  aatgttagca cagcagaaaa caaagacaaa attaaagtgt cactgttgag
98301  cttctgctca ctagtccaaa aacaagcttc ctattcagtt atcactattc
98351  aaaaaaacta ccaaccaaat tttccacatt tatgatgttc gcatatatct
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98551  ggcaaaaacc accttgaaat aagtcctgca ctattactta gcctagattc
98601  attatttaat atcttatatt tcatacactt aggtgtccta tctttccaact
98651  agctgtcaca tcaccctggg taaagctatt acagaatgtg ctcaataaat
98701  aattcttgga tagagtaata aaatggccct gacctcaagt agtttgtggg
98751  aagagataaa acaccaacaa aaaatgggaa gagaggagaa atataaaaag
98801  agaaataaaa aattaaaaac attgcaataa tctaaggaaa gtaagctgaa
98851  gctcccattc aatattatgt aagctttcac cttgttgtgc tccatacaca
98901  gaatttataa tcctgcataa tgaatgcaga aaggctattg taataacaat
98951  agcaacagta ccatcttaga aagtaacaaa gttgtcctta cccaagcaaa
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99101  ggaactaatt aacaccaccc aactgcagag taatttactg cctttgggac
99151  cactgagtta ttgatggtga gtcagaaagg cagaggagac aagcttcagc
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99301  agtgtagatg aactcaacac agcagccaac atccgcctct gggtgcctgg
99351  cactctcacc aaaggacgga gccatgactg tagagtgggt catacacaga
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99451  acccttagtt aactacattc ccggctttgg aatgttcttg ttaaaaaggg
99501  attttgtctt tctacactga ggctagggta tgtttaaaca aaatttgcct
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99651  tcccagcact ttgggaggcc aaagagagtg gatcacctga ggtcaggagt
99701  tcgagaccag cctggccaac atattgtgaa accccctcta ttttaaaaat
99751  acaaaaatta gttgggcgtg gtgctgcatg cctgtagtcc cagctacctg
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100101 tttaatcact catttttttt cctctgaatt cccactaaaa cagtactaat
```

FIGURE 1AG

100151 ctcatatatg tggtggtaaa tgtgtttatt gatttcattc tattaaaaaa
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100251 tataaattgt cattttcaga gaactgaatt tacctctgaa tccatctgtc
100301 cagaataagc caatattctc accttgaggt tttatgtggt tctcccttcc
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100451 ttatctgagg ttttgagatt atctatacat cttgctgcct ctagttactc
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100701 cttgtgctgt gagccaccga gtgctttttc tgaaccactc ctgtgtggtt
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100901 gcatgtgttg ttaaactaaa ctcaataaga ctagattttg gtttttttcc
100951 aacatagtca acttgtgtcc ttattggcaa aatgttccat tgtttcaaaa
101001 acaatctttc caaaatggtc tctccttctg ttcacattta ttgatagagg
101051 aaacggattt agtcttctaa caacacatca taggacttaa aataagaaac
101101 gtacttttct ttcgtttctt acaaaccagc aatctagaat cttttcttct
101151 gttttgttga acatatattc tatctgacaa ttggttacct atatcaacta
101201 taaatgcaga tgtttcacac aaaccaagaa cttacgtttt caaattccaa
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101551 atggctttgt ttttataaaa gaatccctga gcactttcct attcgtgaaa
101601 tgcttagtaa tgtgctgctc tatttccctc actcctagta agttctgtag
101651 taataagcag aagctcttca gaatgtacac ctcacggaag cagaggtacc
101701 cagcatccgg gctattgaca tgagatttga gaatgccaac taacctcagg
101751 tgcatgacca ggttacaccg ccaccccacc tgagccctgt tcagagactc
101801 actctttcta gggacttctt gaatgaggtt ttcaacccgc ttgaaatttt
101851 ccttgttgcc tgttgcctgc tttgatactc tccaccgctg ggacaaatag
101901 tcggcgtccc gcgtagaact ggcagtcagc cctttggcgc ctccttgtgg
101951 ttggacaact gctgagctgc tgcacgcact ggattgttat ggctcagttg
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102051 ctaaaaccct aattaagtat aacaataact acagcattct aagtcccaga
102101 ggattactgt ggggttatga tgatgccaca cagttgcctg gcagagaaca
102151 gcccggtagta gactgcatgc taggccattt gaataacctg tacatctggt
102201 tcctagagat gagagaattc tctcttgcag ggtgacagtg caggctctgc
102251 tgagcgtggt cctcagctgt aactgtggga ctgtacccta agagagatgc
102301 tccgatcaat gacccacgca attttttttt tactttctgc aaagcaagac
102351 ctccttgttg gtctcttggg gataatcctt ggcattcttc ctaaaaatac
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102451 gcaggaaaat aatgaagact tcagtgtttc agtgaagagt ctatattttt
102501 aatcaattca atgtgtgttt tcagtaacag tcacctgatc agcttaatag
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102751 tttctaattt aacatgtaat atgccgagtt tattttaaaa taattcttgg
102801 gaatctttaa aataatagac attagcaaat atccatgtag ttgagaagga
102851 caaaagggaa atgttactta gaatttattt ttgtcaactt taagtgcttt
102901 aaatgatact aagatttaga gaatattact cacattttcc aatttattca
102951 taaggtaatg tcaaaatggt tcatagaggc aatttttaaa aatattttta
103001 taggtatgat ttttaaaata cttttattat aaacaaacta tggtggattg
103051 aatgctaata ctttcatttt ggatgttttt acttttttag taattgaatt
103101 tttttaattt ttcacattaa gtgcttttat gatggtttat ccatttctta
103151 tgtatttagt tgacatagaa aagagatata tcttgaaagt tggagaaaat
103201 aatttgatat taactaaaac caacctttta tagtaattag catctgttag
103251 ttccagaaaa ggtaatagat aaaatcaaat atagtgagga ccaattgtaa

FIGURE 1AH

103301 tgatatctat gtcaacttga gctattcatt aatctgaata aaggtgcaga
103351 agtgagcata tgcttcctga actagatcat tgtaaattta aatcatggaa
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FIGURE 1AI

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FIGURE 1AJ

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109751	ttgccgctgc	tctttcaact	tcaatcggtc	agattcccct	tcccatataa
109801	gccacttgac	catgaccatg	ccactatccc	atctttctcc	cagcctcagc
109851	tgccaaacct	ctcaactaca	tcatctcaag	gcagccagag	ctagaagatt
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FIGURE 1AK

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112951  atttacttct cacagttctg gaagctggaa gtccaagacc atggtgctgg
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116151 tttgccatgt ataatgcata acaacaattt ctgaactcca aaagcataga
116201 aacctcagaa taacattacc tgggaaaaat taatctctct acctccagct
116251 accaagagaa tcatttgcac atgaaacccct gagatttgcg tctttcatta
116301 atctaatgca gtagcaattg ttataccaca tcgttctatt ggaattgatg
116351 actaatcatt tccaaaactc ttttgaaact attgttccca taattttgtg
116401 ttttgattga aaaatgtcat gaccctatat ctcttcatgt tatctgttgc
116451 atagctaacc ctctccctca gatttagtgg cttaaaacag caaccatttg
116501 tttagcccac aattctgtta ggcagttctt ctggtcttaa gtgaactgac
116551 tcatgctctg tgttcagctg ctgtgttggc tggtgctgac tggactaagg
116601 tggtctcagt tagaattact gctctttgct catgtggtct ctcatcctcc
116651 agcaggctgg gctggttcac atggtggtgg tgggttccca agagcagtac
116701 attgacatct gaaggcctct tgaagttcag gctcaaccta tcacagtata
116751 atgtccacta tgtcctgttg gtcaaagcaa atggcaagga cagcccacat
116801 gcaagagaca gagaaagaga ttccacctct tcatgtgaga agctgcaagt
116851 gtcgtggcca gtattgcaat ctaccatccc agccatttaa agcttatttg
116901 cttttagtat tttcaacatc ctgttggttc tatgaagaca gtgtcagtgt
116951 ctaattgact tttttatttc tccctgtagt atccttcact caaagagcct
117001 aagaaagaaa aggaaaatag cattgttagc acctcatgta tcgaggcatt
117051 ggctagacat ttttatgaa ttggctcatt taatacacac atagccattt
117101 tgcagataag gaaattgaga ctcagaaaat gtaaataact tgcccacata
117151 attcagtcta aatgccaaaa ctggggtttg aagttgcact taggtctaag
117201 tttcaaagctt tttatgttct accatgcatg ctgcttagca tgttttcttt
117251 catataattc atgctgctaa tgaaacagta taaaccagct gtatgttaac
117301 tgctagtgaa atgattttatt gtcttctttt tcagtaaata tggcaagtct
117351 gctcaattta ttcccttttat cattgcatac actacaaata ttctctccct
117401 ataccttcac atgtcaatta aggtatgcaa cagtaatttc cattttcttt
117451 aaacaatgct tatgttacca tctctagaca agttagtcca gatgattttg
117501 gggttaacat gttggcattt cctggcacta ttactgctag ctgaataagc
117551 gttgaaagtt ggggaaaaat ttaccagatc tgtattagct ttttcgcaca
117601 ctgatataaa gaactacctg agactgggtg atttataaag aaaagtttaa
117651 ttgactcaca gttccacaac ctgtacagga agcacgcctg ggatgcctca
117701 agaaacttac agtcatgtca gaagagcgaa agggaaggaa gcgtgtcttt
117751 acgtggtagc agaagagaaa gagacagaga gaatgagaaa gtgagagtga
117801 agggggaagt gccacacttt taaaccataa tccaccccca tgatccattc
117851 acctcccacc cagtccctcc cccaacattg ggaataacaa ctcaacatga
117901 gatttgggtg gggatacaga gcgaaaccat atcaagatct atttagaatt
117951 ctccagcaga tttgattaac aatatagatt tgtgattctg caatttgtag
118001 ggtcattata aaacatggct gccttgattg caatcagata tctctgaata
118051 tggttcaaag gaaacagatc tcgttcttgt ggagatagga ttacataact
118101 ccctctcagt cattttgcca ttgattcaga atgtttctcc ctaagatgaa
118151 gtactgtttt agcttagaat ggtaacagca attcatcacc aggcacagtg
118201 gctcacacct gtgatcccca cactttggga ggcccaggcc tgtggatcac
118251 ttgagcccag gagttagaga ctagcctagg caacatggca aaaccccatc
118301 tctacaaaaa atgtaaaaat tagctgggca tggtggcaca ggcctatagc
118351 cccagccact tgggaggctg agaaatggga ggatcttttg agcccaggag
118401 gttgaggctg cagtgagcca tgatcgcatc actgcactcc atcctgggca
118451 acagaacaag tccctgtctc aaaaaaaaaa aaaaaaaaaa aaaaaaagca
118501 attcattgat ctcatctagt ttgactagtt caattataca tgtgagaagg
118551 ctatctgaga tgatgtcagg tgtggagcag tgactatccc agtgatctga
118601 atgtgattga ccacttggct tcaccaggat tatctcactg tttggttcta
118651 ataaaggcag tcattctagt ctatgagttt acctcccttt tgctacaaac
118701 acttcagtga tatactattg aaactataaa aatccataaa aattggtttt
118751 tgtatgtgag ttttaaaaaa ttgttttcac caggctgtga gttttatgtc
118801 tttgttttct attgggatac taatagtgct atgactatag tatgttctca
118851 aggaaattct tatgaaaatt gaattaaccc gacacagtgc atggttttgg
118901 agtaaaacag aacttgtttt aaatcctagt tcccccacta ggttgggtga
118951 gatgagacaa acgacttaac ctcactgcca ctttaatttg ttctctctct
119001 ctctttaggg tggtagaaat gatacctacc taatagggtt acgtgagtaa

FIGURE 1AM

119051 taataagata taatgtgtgt aaaattcttg tacaatgccc agcacagaat
119101 aggtgctcaa tatattaaat atattgttat tatttactaa ttaattaatg
119151 ctgatttctg cattaatttt gactaattga aatcctggac ttgcttaatt
119201 tgcatgtatt tgtcttccct tcttccagta cttgatggca atttctacct
119251 gtggtaaatg gaacgttaaa agttatatgc ttatacaaac tttagtcctt
119301 tattccttgg agtgagtttt aagagtcctc atgttgaata attcatgtaa
119351 tcacagaaat aatactatgt atcagggacc gcttccttta ttaaagataa
119401 aggcagtgga aatactgcct ttgtcagaaa tacttcagtt actctgagag
119451 agagagacat ttgtttacta tatgacagca cagtgcatgg cadataatag
119501 aagtttggaa aatatttatt ttgaatgaac gaataatgaa cacattgtga
119551 acaaataaat ggtttactat ttaattattc aggaatcaat taagctttat
119601 taataaaaat tgtttggggg ttttaaaaag cccacacaca aatgagaggc
119651 atcacagagg caaacggtat gacattatta aaatcgttat tgctgaatca
119701 cagttcagca ataagcaagt gtttgaggca ttcaaataag tgagtatttg
119751 agtgactcta agaagataat gaaactcctc cactgtttta cagttgcaat
119801 aatttttaag gaacatataa aaacatattc tagtgtttcc atttgaataa
119851 agatagtata tataacatat gcaattaaaa agaagaaaga aaacaaattt
119901 taatgtgttt ttctttttac cttatgggca gttactagat gtatnnnnnn
119951 nnnnagcttc atcttgcccg tagaaaacag ttcagaaaag tattcatatt
120001 taaaactggg gaggctgtag aaaaagaaga aagaataata ttggcaagac
120051 aattggctga ccttatacat atcttggttt atcagcttac tctgtgagta
120101 tcccgccatt tccacgtgag aaaaattcag caacatgttt caaattgcgg
120151 atggtggtgt tatttaactg gcaatattbt cttgcagCTG ACACAGCCCT Exon 11
120201 TGGCACTGAT GATGTATATG ATGAAAAAGG ATGCCAGTGT GATGTATCAG
120251 TGGAAGACCT CACCCCACCA CTTAAAACTG TCATTCGAGC TATCAGgttg
120301 gtgaaaatct tgaacaacgt gattcagaga catacttatg attaattgaa
120351 ttactatgtt gctaagttct ttttctgcag gtaaatatcc tggaataacc
120401 actttccctt tcctattcat nnnnnnnnnn aatagagtgt tttgcaaaca
120451 catttgtatc tcaaaaatgc atgtagttcc ataaaagacc attttaacag
120501 cctttatatt ttttaaggga tgctattact agatgttgta tcttggactt
120551 ctggagattg catggaaaag ttagaattgc attttgactt taacttacat
120601 tcagggtttc aacggdcatt aaaaaggcaa aacacttagt gttcagcctc
120651 tttttagtg tgttttteta ttcttaaggt gttgtctcac atgagatgtt
120701 cttaaattgt ccactgtaat ctcaggcttt tatattacac atctgcagaa
120751 gccaaaaata atttgatgca tgactttccc ccccagagtt tcttattata
120801 tttactggta aactattttg gtaacttata ttaacagagt tataaagatt
120851 aatatgtaat atgttctcat acagAATTAT GAAATTTCAT GTTGCAAAAC Exon 12
120901 GGAAGTTTAA GGAAACATTA CGTCCATATG ATGTAAAAGA TGTCATTGAA
120951 CAATATTCTG CTGGTCATCT GGACATGTTG TGTAGAATTA AAAGCCTTCA
121001 AACACGgtaa gcaatggaag tgtcattcct tgtaaaggaa tgggcataga
121051 acctatctag gaagaacttc tctttagtag agtaaacctc tgaactccat
121101 atttttcatt catttttagt gggcaaatgg aatttgcttt aaacattgat
121151 tttattttgc ttttaacata gatataactc aggcattcaa agcatccaac
121201 tgtctcattt tccttatctg taaaaatggg aagaaagtta gttcttgcct
121251 tatagggttg ttcatgaggat tgaacaagtt aatgcatgta attcataaca
121301 tgtaacaggc ctggtactgt gtctaataaa catcaatggt tgttgctgat
121351 gtttgaatta ttactgctgc tgatcctaaa ttatctaaat tccatttatt
121401 atctaaattc taatcatcct ttgggaataa cgtactattt ctccttcatt
121451 aagtttcatc caaccatcca acctgtgaag acgggccttt ctctgacctt
121501 tatacagtag cagagtctac tgcagagcac aagagcactc agaatctcgg
121551 tgtgctgggc caaagttgag acttggccct tgtgttgttt cctggttgca
121601 agtgtgttca ccttgdtctg gactaagact gaggtccttc attcatgtcc
121651 tgtacggttc tacaaatata ctatcctcct agtagcatct tattgagtga
121701 ttaaaagaaa tgaattccac atgttaattc caaccacata tggttgattg
121751 tgattatctc aaagccaaaa tattcagtaa attcagtttt ttaagagcct
121801 tgctttatta ccagcacaaa ttaccagcat ttgtgattgt atagtgccca
121851 aaatgcaagg actgagactt gacttttttt tatgcccccc agcacactta
121901 gcccagtgtg aggcatatas tgggccctta gtaaaatacc tgttcatcaa
121951 ttgttataga aataacaatt tgttaattca tttagcaggt aattattgag
122001 cccatcatgt gtgccaggac ctgtggacat ccagagattg ataaataat
122051 gacccagacc ttgtagagtt tgcagtttag taaattagat gnnnnnnnnn
122101 ngaacatctg aacatgacca gagattgtgg tcatattgca atctctgcct
122151 agatggccat ggccttctaa gttctttaat aaaactgtct acagctccca

122201 aggttttata aagttgaact gctacagaat ttatagaacc aatcttgggt
122251 ttctagctca tgtatcttct ccaacttgaa ctccgaaaga aaaagaccat
122301 ggctttctta tctgcttatc tttcacacat gtacaataga tgctcataga
122351 ataatctgtt ctattaatgt aagatctcta tagttatgat ttttgtcata
122401 ttttgaaatg gttaaattca ggaactgcct gatcagaggt agaaacatat
122451 tactttgtag tttaggacac ttttactccc agaagatcac ccatcagtga
122501 tttcatcttg gaccagaata atgagaaaat taatttcatg tgtaatctca
122551 tgttcaaata agcatatcaa ctggaacaag ttctttctta tttcatctta
122601 cataaattga agataactgt atttaatttt tttttccaaa actcttcatt
122651 ctgacctagg gcaatctcca ccttcagccc tcataatcag atctcctctt
122701 tctctgatag TGTTGATCAA ATTCTTGGAA AAGGGCAAAT CACATCAGAT
122751 AAGAAGAGCC GAGAGAAAAT AACAGCAGAA CATGAGACCA CAGACGATCT
122801 CAGTATGCTC GGTCGGGTGG TCAAGGTTGA AAAACAGgta caactcaact Exon 13
122851 acgctgggta tctttttagc cagaattttt ttaatcaaaa tttattatag
122901 gcaattgtat gtattccagt gattatttta aaataaataa aatcacaaaa
122951 agagtgaata aaattaaatt ttctttgtgt gtagacagtg ctctctgaaa
123001 cactctggat ttccctttaa ggaatagaaa atctcatctc atcaattaat
123051 agttaattgg aaacaactat agatttccaa tagttgaaaa tcgtttaaaa
123101 ataacaaaga tctattcttc atttgtgttt cagttgtttt tattgtttct
123151 tttttaggtc attaattttt tttttttttt tttnnnnnnn nnngggacta
123201 tgggcatgca ccaccacacc tggctgattt ttgtattatt tttggtagag
123251 acgaggtctc accatgttgc ccaggctggt ctcaaactcc tgggctcaat
123301 tctcctgcct cagtttccca aagtgctggc attacaggca tgagccactg
123351 cacccagcct ggaatggaaa gtcttaaagt tgcattttta tagtgcttat
123401 atgactttta agaggcacta tttaaagaag tggtgggga gagatgctaa
123451 taaagactgt atagaagcca aagtgtccct ctcttcctaa gtcctcctct
123501 ggccccatca ttgctaaatg ttacattcac taagggccaa gactgcatcg
123551 tactttatat tcaatatttc tttaaatgtg ttggcacacc ttgacttcat
123601 ttttcaaaat taaaaaatga agtccattct taataacaga ttatactcat
123651 gtgtaaccat tttcctcact tctagGTACA GTCCATAGAA TCCAAGCTGG
123701 ACTGCCTACT AGACATCTAT CAACAGGTCC TTCGGAAAGG CTCTGCCTCA
123751 GCCCTCGCTT TGGCTTCATT CCAGATCCCA CCTTTTGAAT GTGAACAGAC
123801 ATCTGACTAT CAAAGCCCTG TGGATAGCAA AGATCTTTCG GGTTCCGCAC
123851 AAAACAGTGG CTGCTTATCC AGATCAACTA GTGCCAACAT CTCGAGAGCC
123901 CTGCAGTTCA TTCTGACGCC AAATGAGTTC AGTGCCCAGA CTTTCTACGC Exon 14
123951 GCTTAGCCCT ACTATGCACA GTCAAGCAAC ACAGGTGCCA ATTAGTCAAA
124001 GCGATGGCTC AGCAGTGGCA GCCACCAACA CCATTGCAAA CCAAATAAAT
124051 ACGGCACCCA AGCCAGCAGC CCCAACAACT TTACAGATCC CACCTCCTCT
124101 CCCAGCCATC AAGCATCTGC CCAGGCCAGA AACTCTGCAC CCTAACCCTG
124151 CAGGCTTACA GGAAAGCATT TCTGACGTCA CCACCTGCCT TGTTGCCTCC
124201 AAGGAAAATG TTCAGGTTGC ACAGTCAAAT CTCACCAAGG ACCGTTCTAT
124251 GAGGAAAAGC TTTGACATGG GAGGAGAAAC TCTGTTGTCT GTCTGTCCCA
124301 TGGTGCCGAA GGACTTGGGC AAATCTTTGT CTGTGCAAAA CCTGATCAGG
124351 TCGACCGAGG AACTGAATAT ACAACTTTCA GGGAGTGAGT CAAGTGGCTC
124401 CAGAGGCAGC CAAGATTTTT ACCCCAAATG GAGGGAATCC AAATTGTTTA
124451 TAACTGATGA AGAGGTGGGT CCCGAAGAGA CAGAGACAGA CACTTTTGAT
124501 GCCGCACCGC AGCCTGCCAG GGAAGCTGCC TTTGCATCAG ACTCTCTAAG
124551 GACTGGAAGG TCACGATTAT CTCAGAGCAT TTGTAAGGCA GGAGAAAGTA
124601 CAGATCCCCT CAGCTTGCCT CATGTCAAAC TGAAATAAGT TCTTCATTTT
124651 CTTTCCAGGC ATAGCAGTTC TTTAGCTATA CATATCATTG CATGAACTAT
124701 TTCGAAAGCC CTTTTAAAAA GTTGAAATTG CAAGAATCGG GAAGAACATG
124751 AAAGGCAGTT TATAAGCCCG TTACCTTTTA ATTGCATGAA AATGCATGTT
124801 TAGGGATGGC TAAAATTCCA AGGTGCATCG ACATTAACCC ACTCATTTAG
124851 TAATGTACCT TGAGTTAAAA AGCCTGAGAA ACCAAACACA GCTAATGCTA
124901 TGGGGTGTAT GAATATGTCA AGTTTAGGTC ATTTAGAAGA TTTGACACTG
124951 TATTTTGAAA TTATGGGAGT AAACACCTTC AAATTTCAGG CATTTCTGCT
125001 TTGTGACTAA ATACAAACTA CATTTTCAAG ATTAGCCCAT AATGTATATT
125051 TAAACACAAT GGCTATCAAC AGCTGCTAAT AAGGTATCAA CTAAAGCAGA
125101 ATTGGGGAAT AATAGAAATG GCTGCTTATT TCAAGATATA TTTGCCAACC
125151 CATTCCTATT CAGTCATTTT ATTATTAATG TAATTTGAAT GTCAATTTGT
125201 GTGCTTTTGG TGATTTAGCG CTGTGGCAAG CAATTTTGCA CATCATTTTC
125251 ATGTTGTTCT TTATGACAAG AATGTTCTTC AATTAGAAAA TGTGCAAATA
125301 ATGAAATTCA GGGCCAGTGA GGCAAATAGA CTATCTGACA TATTTGACTT

FIGURE 1AO

125351 TATGAAAACA TATTGCCTGA TGGCAGAATC AACTTTATAA GTGGTCAACT
125401 TCTACACAAG CGTATGAAAT ACTGGTCAGT AGAACAGCCA TTGTGATTGG
125451 ACTGGTTTCT CTGCAATGGC GCCAACCCCA GCCTTGCCAA TACTGCCTAT
125501 GTAAAGGGCA AGTGTGAGAA GCTATTCTCA TTTCGCTGAC ATACAGGTAG
125551 GACTATGGGG GATGGGACAT TTGAGTGGGA CTGAGATAGG AAAGGCTTGA
125601 AAAGAACCCA GAAACACCAC CAGGAAGTTG GCAAAGTAAA AGAAAATGAC
125651 TTCCCCCTCA AAGGGCAATG AGAGGGAGAG AAACAAACCA AAATAGAAGA
125701 ACTAGACTTT TTAGGAAATG AGTATTGCTA GGGAATTCAA CTACCTAATC
125751 TTCCCTTATT CTTATATATA AGCAGAGAAT TTTTGCAAGG TATTTATTTT
125801 TTAATATGCC CTGAAGGTCT TTTGCTATTA TGTGTACATT TTGCATATGA
125851 AAGTCTAAAA GGAAACTTCC TTTACTTTTT ATACTGTAGT GAAAATTTTC
125901 TATTCTTCCC AAGAAGTTTG TCCCAAATCT GAAATTACTG GTTCAATTTC
125951 CTGATATAAA

FIGURE 2A

KCN6q cDNA

1 CTGGAGTGAGGCGCGGGAAGATGCCTGGTCCTTGCCTCGCGGACTTGGCA 50

51 GCCGCGTCCTGCGGGTCTGTCCACTGAACTGCTGAGGACTGCGGCGGTGG 100

101 CCTGAGGGAGAGCCGCCGGGGCAAGCAGGGGGCCCGGATGAGCCTGCTGG 150
1 M S L L G 5

151 GGAAGCCGCTCTCTTACACGAGTAGCCAGAGCTGCCGGCGCAACGTCAAG 200
6 K P L S Y T S S Q S C R R N V K 21

201 TACCGGCGGGTGCAGAACTACCTGTACAACGTGCTGGAGAGACCCCGCGG 250
22 Y R R V Q N Y L Y N V L E R P R G 38

251 CTGGGCGTTCATCTACCACGCTTTCGTTTTTCTCCTTGTCTTTGGTTGCT 300
39 W A F I Y H A F V F L L V F G C L 55

301 TGATTTTGTCAGTGTTTTCTACCATCCCTGAGCACACAAAATTGGCCTCA 350
56 I L S V F S T I P E H T K L A S 71

351 AGTTGCCTCTTGATCCTGGAGTTCGTGATGATTGTCGTCTTTGGTTTGGA 400
72 S C L L I L E F V M I V V F G L E 88

401 GTTCATCATTCGAATCTGGTCTGCGGGTTGCTGTTGTCGATATAGAGGAT 450
89 F I I R I W S A G C C C R Y R G W 105

451 GGCAAGGAAGACTGAGGTTTGCTCGAAAGCCCTTCTGTGTTATAGATACC 500
106 Q G R L R F A R K P F C V I D T 121

501 ATTGTTCTTATCGCTTCAATAGCAGTTGTTTCTGCAAAAACTCAGGGTAA 550
122 I V L I A S I A V V S A K T Q G N 138

551 TATTTTTGCCACGTCTGCACTCAGAAGTCTCCGTTTCCTACAGATCCTCC 600
139 I F A T S A L R S L R F L Q I L R 155

601 GCATGGTGCGCATGGACCGAAGGGGAGGCACTTGGAAATTACTGGGTTCA 650
156 M V R M D R R G G T W K L L G S 171

651 GTGGTTTATGCTCACAGCAAGGAATTAATCACAGCTTGGTACATAGGATT 700
172 V V Y A H S K E L I T A W Y I G F 188

701 TTTGGTTCTTATTTTTTCGTCTTTCCTTGTCTATCTGGTGGAAAAGGATG 750
189 L V L I F S S F L V Y L V E K D A 205

751 CCAATAAAGAGTTTTCTACATATGCAGATGCTCTCTGGTGGGGCACAATT 800

FIGURE 2B

206 N K E F S T Y A D A L N W G T I 221

601 ACATTGACAACTATTGGCTATGGAGACAAAACTCCCCTAACTTGGCTGGG 650
222 T L T T I G Y G D K T P L T W L G 238

651 AAGATTGCTTTCTGCAGGCTTTGCACTCCTTGGCATTTCTTTCTTTGCAC 700
239 R L L S A G F A L L G I S F F A L 255

701 TTCCTGCCGGCATTCTTGGCTCAGGTTTTGCATTAAAAGTACAAGAACAA 750
256 P A G I L G S G F A L K V Q E Q 271

751 CACCGCCAGAAACACTTTGAGAAAAGAAGGAACCCAGCTGCCAACCTCAT 800
272 H R Q K H F E K R R N P A A N L I 288

801 TCAGTGTGTTTGGCGTAGTTACGCAGCTGATGAGAAATCTGTTTCCATTG 850
289 Q C V W R S Y A A D E K S V S I A 305

851 CAACCTGGAAGCCACACTTGAAGGCCTTGCACACCTGCAGCCCTACCAAG 900
306 T W K P H L K A L H T C S P T K 321

901 AAAGAACAAGGGGAAGCATCAAGCAGTCAGAAGCTAAGTTTTAAGGAGCG 950
322 K E Q G E A S S S Q K L S F K E R 338

951 AGTGCGCATGGCTAGCCCCAGGGGCCAGAGTATTAAGAGCCGACAAGCCT 1000
339 V R M A S P R G Q S I K S R Q A S 355

1001 CAGTAGGTGACAGGAGGTCCCCAAGCACCGACATCACAGCCGAGGGCAGT 1050
356 V G D R R S P S T D I T A E G S 371

1051 CCCACCAAAGTGCAGAAGAGCTGGAGCTTCAACGACCGAACCCGCTTCCG 1100
372 P T K V Q K S W S F N D R T R F R 388

1101 GCCCCTCGCTGCGCCTCAAAAGTTCTCAGCCAAAACCAGTGATAGATGCTG 1150
389 P S L R L K S S Q P K P V I D A D 405

1151 ACACAGCCCTTGGCACTGATGATGTATATGATGAAAAAGGATGCCAGTGT 1200
406 T A L G T D D V Y D E K G C Q C 421

1201 GATGTATCAGTGGAAGACCTCACCCCACCACTTAAAACTGTCATTCGAGC 1250
422 D V S V E D L T P P L K T V I R A 438

1251 TATCAGAATTATGAAATTTCATGTTGCAAAACGGAAGTTTAAGGAAACAT 1300
439 I R I M K F H V A K R K F K E T L 455

1301 TACGTCCATATGATGTAAAAGATGTCATTGAACAATATTCTGCTGGTCAT 1350
456 R P Y D V K D V I E Q Y S A G H 471

FIGURE 2C

```
1551  CTGGACATGTTGTGTAGAATTAAAAGCCTTCAAACACGTGTTGATCAAAT  1600
472   L  D  M  L  C  R  I  K  S  L  Q  T  R  V  D  Q  I  488

1601  TCTTGGAAAAGGGCAAATCACATCAGATAAGAAGAGCCGAGAGAAAATAA  1650
489    L  G  K  G  Q  I  T  S  D  K  K  S  R  E  K  I  T  505

1651  CAGCAGAACATGAGACCACAGACGATCTCAGTATGCTCGGTCGGGTGGTC  1700
506     A  E  H  E  T  T  D  D  L  S  M  L  G  R  V  V   521

1701  AAGGTTGAAAAACAGGTACAGTCCATAGAATCCAAGCTGGACTGCCTACT  1750
522   K  V  E  K  Q  V  Q  S  I  E  S  K  L  D  C  L  L  538

1751  AGACATCTATCAACAGGTCCTTCGGAAAGGCTCTGCCTCAGCCCTCGCTT  1800
539    D  I  Y  Q  Q  V  L  R  K  G  S  A  S  A  L  A  L  555

1801  TGGCTTCATTCCAGATCCCACCTTTTGAATGTGAACAGACATCTGACTAT  1850
556     A  S  F  Q  I  P  P  F  E  C  E  Q  T  S  D  Y   571

1851  CAAAGCCCTGTGGATAGCAAAGATCTTTCGGGTTCCGCACAAAACAGTGG  1900
572   Q  S  P  V  D  S  K  D  L  S  G  S  A  Q  N  S  G  588

1901  CTGCTTATCCAGATCAACTAGTGCCAACATCTCGAGAGGCCTGCAGTTCA  1950
589    C  L  S  R  S  T  S  A  N  I  S  R  G  L  Q  F  I  605

1951  TTCTGACGCCAAATGAGTTCAGTGCCCAGACTTTCTACGCGCTTAGCCCT  2000
606     L  T  P  N  E  F  S  A  Q  T  F  Y  A  L  S  P   621

2001  ACTATGCACAGTCAAGCAACACAGGTGCCAATTAGTCAAAGCGATGGCTC  2050
622   T  M  H  S  Q  A  T  Q  V  P  I  S  Q  S  D  G  S  638

2051  AGCAGTGGCAGCCACCAACACCATTGCAAACCAAATAAATACGGCACCCA  2100
639    A  V  A  A  T  N  T  I  A  N  Q  I  N  T  A  P  K  655

2101  AGCCAGCAGCCCCAACAACTTTACAGATCCCACCTCCTCTCCCAGCCATC  2150
656     P  A  A  P  T  T  L  Q  I  P  P  P  L  P  A  I   671

2151  AAGCATCTGCCCAGGCCAGAAACTCTGCACCCTAACCCTGCAGGCTTACA  2200
672   K  H  L  P  R  P  E  T  L  H  P  N  P  A  G  L  Q  688

2201  GGAAAGCATTTCTGACGTCACCACCTGCCTTGTTGCCTCCAAGGAAAATG  2250
689    E  S  I  S  D  V  T  T  C  L  V  A  S  K  E  N  V  705

2251  TTCAGGTTGCACAGTCAAATCTCACCAAGGACCGTTCTATGAGGAAAAGC  2300
706     Q  V  A  Q  S  N  L  T  K  D  R  S  M  R  K  S   721

2301  TTTGACATGGGAGGAGAAACTCTGTTGTCTGTCTGTCCCATGGTGCCGAA  2350
```

```
722   F  D  H  G  G  E  T  L  L  S  V  C  P  H  V  P  K      738

2351  GGACTTGGGCAAATCTTTGTCTGTGCAAAACCTGATCAGGTCGACCGAGG   2400
739    D  L  G  K  S  L  S  V  Q  N  L  I  R  S  T  E  E    755

2401  AACTGAATATACAACTTTCAGGGAGTGAGTCAAGTGCCTCCAGAGGCAGC   2450
756     L  N  I  Q  L  S  G  S  E  S  S  A  S  R  G  S      771

2451  CAAGATTTTTACCCCAAATGGAGGGAATCCAAATTGTTTATAACTGATGA   2500
772   Q  D  F  Y  P  K  W  R  E  S  K  L  F  I  T  D  E     788

2501  AGAGGTGGGTCCCGAAGAGACAGAGACAGACACTTTTGATGCCGCACCGC   2550
789    E  V  G  P  E  E  T  E  T  D  T  F  D  A  A  P  Q    805

2551  AGCCTGCCAGGGAAGCTGCCTTTGCATCAGACTCTCTAAGGACTGGAAGG   2600
806     P  A  R  E  A  A  F  A  S  D  S  L  R  T  G  R      821

2601  TCACGATCATCTCAGAGCATTTGTAAGGCAGGAGAAAGTACAGATGCCCT   2650
822   S  R  S  S  Q  S  I  C  K  A  G  E  S  T  D  A  L     838

2651  CAGCTTGCCTCATGTCAAACTGAAATAAGTTCTTCATTTTCTTTCCAGGC   2700
839    S  L  P  H  V  K  L  K                                846

2701  ATAGCAGTTCTTTAGCCATACATATCATTGCATGAACTATTTCGAAAGCC   2750

2751  CTTCTAAAAAGTTGAAATTGCAAGAATCGGGAAGAACATGAAAGGCAGTT   2800

2801  TATAAGCCCGTTACCTTTTAATTGCATGAAAATGCATGTTTAGGGATGGC   2850

2851  TAAAATTCCAAGGTGCATCGACATTAACCCACTCATTTAGTAATGTACCT   2900

2901  TGAGTTAAAAAGCCTGAGAAACCAAACACAGCTAATGCTATGGGGTGTAT   2950

2951  GAATATGTCAAGTTTAGGTCATTTAGAAGATTTGACACTGTATTTTGAAA   3000

3001  TTATGGGAGTAAACACCTTCAAATTTCAGGCATTTCTGCTTTGTGACTAA   3050

3051  ATACAAACTACATTTTCAAGATTAGGCCATAATGTATATTTAAACACAAT   3100

3101  GGCTATCAACAGCTGCTAATAAGGTATCAACTAAAGCAGAATTGGGGAAT   3150

3151  AATAGAAATGGCTGCTTATTTCAAGATATATTTGCCAACCCATTCCTATT   3200

3201  CAGTCATTTTATTATTAATGTAATTTGAATGTCAATTTGTGTGCTTTTGG   3250
```

FIGURE 2E

3251 TGATTTAGCGCTGTGGCAAGCAATTTTGCACATCATTTTCATGTTGTTCT 3300

3301 TTATGACAAGAATGTTCTTCAATTAGAAAATGTGCAAATAATGAAATTCA 3350

3351 GGGCCAGTGAGGCAAATAGACTATCTGACATATTTGACTTTATGAAAACA 3400

3401 TATTGCCTGATGGCAGAATCAACTTTATAAGTGGTCAACTTCTACACAAG 3450

3451 CGTATGAAATACTGGTCAGTAGAACAGCCATTGTGATTGGACTGGTTTCT 3500

3501 CTGCAATGGCGCCAACCCCAGGCTTGCCAATACTGCCTATGTAAAGGGCA 3550

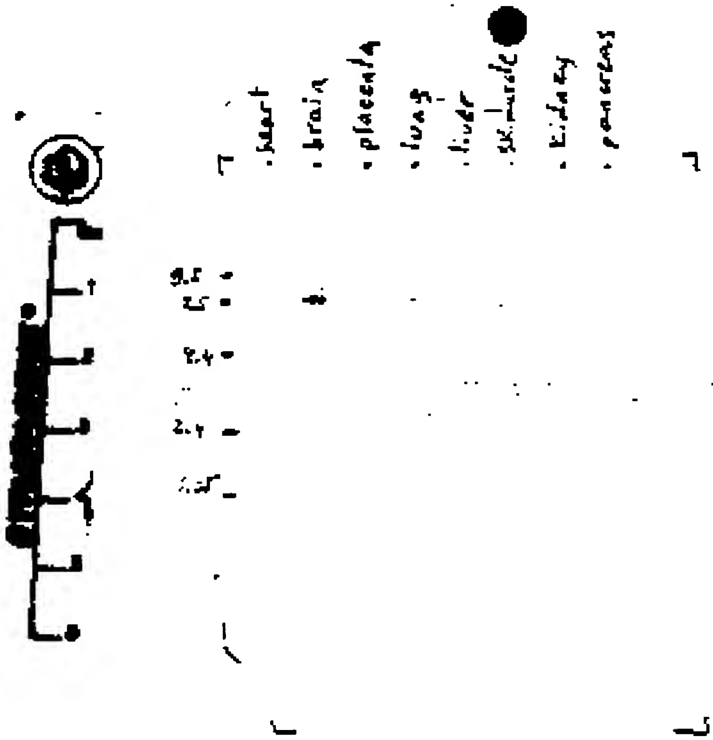
3551 AGTGTGAGAAGCTATTCTCATTTCGCTGACATACAGGTAGGACTATGGGG 3600

3601 GATGGACATTTGAGTGGGACTGAGATAGGAAAGGCTTGAAAAGAACCCA 3650

3651 GAAACACCACCAGGAAGTTGGCAAAGTAAAAGAAAATGACTTCCCCTCA 3700

3701 AAGGGCAATGAGAGGGAG

FIGURE 3A



probe: DL/ER PCR fragment.

FIGURE 3B

RT-PCR analysis of the KCN6q gene expression in human tissues

KCN6q cDNA
22 cycles

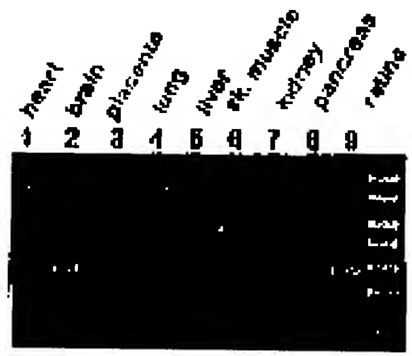


FIGURE 4A

```
KCN6q_     ..............................................MS.....LLGRLG........
KCNQ4_     MAEAPPRRLGLGPPPGDAPRAELVALTAVQSEQGEAGGG SPRRLGLLGSPLPPGAPLPG
consensus  maeapprrlg.pppgdapraelvaltavqseqgeaggg SprrlgLLG PL pgaplpg

KCN6q_     YTE.SGS.SR.RN...VK.YRRVQNYLYNVLERPRGWAFIYHAFVFLLVFGCLILSVFST
KCNQ4_     PGSGSGSACGQRSSRAAKRYRRVQNYVYNVLERPRGWAFVYHVFIFLLVFSCLVLSVLST
consensus    Sgs SaC qR saa KrYRRvQNYlYNVLERPRGWAFIYH FVFLLVF CLILSV ST

KCN6q_     IPEHTKLASSCLLILEFVMIVVFGLEFIIRIWSAGCCCRYRGWQGRLRFARKPFCVIDTI
KCNQ4_     IQEHQELANECLLILEFVMIVVFGLEYIIRVWSAGCCCRYRGWQGRFRFARKPFCVIDFI
consensus  I EH  LA  CLLILEFVMIVVFGLEfIIRIWSAGCCCRYRGWQGR RFARKPFCVID I

KCN6q_     VLIASIAVVSAKTQGNIFATSALRSIRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT
KCNQ4_     VFVASVAVIAAGTQGNIFATSALRSMRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT
consensus  V iASiAVV A TQGNIFATSALRSIRFLQILRMVRMDRRGGTWKLLGSVVYAHSKELIT

KCN6q_     AWYIGFLVLIFSSFLVYLVEKDANKEFSTYADALWWGTITLTTIGYGDKTPLTWLGRLLS
KCNQ4_     AWYIGFLVLIFASFLVYLAEKDANSDFSSYADSLWWGTITLTTIGYGDKTPHTWLGRVLA
consensus  AWYIGFLVLIF SFLVYL EKDAN eFStYAD LWWGTITLTTIGYGDKTP TWLGRIL

KCN6q_     AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRRMPAANLIQCVWRSYAADEKS.
KCNQ4_     AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRRNPAANLIQAAWRLYSTDMSR
consensus  AGFALLGISFFALPAGILGSGFALKVQEQHRQKHFEKRR PAAKLIQ  WR Y  De Sr

KCN6q_     .VSIATWKP...SLK.....AHK.......................................TCS
KCNQ4_     AYLTATWYYYDSILPSFRELALLFEHVQRARNGGLRPLEVRRAPVPDGAPSRYPPVATCH
consensus  s   ATW   yds L sfrelAL fehvqrarnggirplevrrapvpdgapsryppvaTC

KCN6q_     .E..TKKEQGEASSSQKLSFKERVRMASPR..GQSIKSRQASVGDRRSPSTDITAEGS.S
KCNQ4_     RPGSTSPCPGE..SSRMG.IKERVRMSSSQRRTGPS.KQQLAPPTMPTSPSSEQVGEATS
consensus  rPgsT     GEasss   s KeRvRMaS qRrtG SiK   A        SPStd  aEgtS

KCN6q_     PTKVQKSWSFNDRTRFRPSLRLKSSQPKPVIDADTALGTDDVYDEKGCQCDVSVEDLTP
KCNQ4_     PTKVQKSWSFNDRTRFRASLRLK...PR..TSAEDAP..EEVAEEKSYQCDVSVEDIMPA
consensus  PTKVQKSWSFNDRTRFR SLRLKsmqPkpv  Ad A gtddV dSK  QCdvsVeDl P

KCN6q_     PLKTVIRAIRIMKFHVAKRKFKETLRPYDVKDVIEQYSAGHLDMLCRIKSLQTRVDQIIGK
KCNQ4_     VKTVIRSIRILKFLVAKRKFKETLRPYDVKDVIEQYSAGHLDMLGRIKSLQTRVDQIVGR
consensus  iKTVIR IRImKF VAKRKFKETLRPYDVKDVIEQYSAGHLDML RIKSLQTRVDQIIGK

KCN6q_     GQITSDKKSREK...ITAEHETTDDLSMLGRVVKVEKQVQSIESKLDCLLDIYQQVLRKG
KCNQ4_     G..PGDRKAREKGDKGPSDAEVVDEISMMGRVVKVEKQVQSIEHKLDLLLGFYSRCLRSG
consensus  Gqi   DEK  RKKgdk   s  E  DdiSMIGRVVKVEKQVQSIE KLD LL  Y    LR G

KCN6q_     .SASALALASFQIPPFECEQTSDYQSPVDSKDLSGSAQNSGCLSRSTSANISRGLQFILT
KCNQ4_     TSASLGAVQVPLFDPDITSDYHSPVDHEDISVSAQTLSISRSVSTNMD.......
consensus  tSASalaLa  QIP Fe s TSDY SPVD DIS SAQt Sgglsrs S Ni rglgfil

KCN6q_     TPNEFSAQTFYALSPTMHSQATQVPISQSDGSAVAATNTIANQINTAPKPAAPTTLQIPP
KCNQ4_     ............................................................
consensus  tpnafsaqtfyalsptmhsqatqvpisqsdgsavaatntianqintapkpaapttlqipp

KCN6q_     PLPAIKHLPRPETLHPNPAGLQSSISDVTTCLVASKENVQVAQSNLTKDRSMRKSFDMGG
KCNQ4_     ............................................................
consensus  plpaikhlprpetlhpnpaglqssisdvttclvaskenvqvaqsnltkdrsmrksfdmgg

KCN6q_     ETLLSVCPMVPKDLGKSLSVQNLIRSTEELNIQLSGSESSGSRGSQDFYPKWRESKLFIT
KCNQ4_     ............................................................
consensus  etllsvcpmvpkdlgkslsvqnlirsteelniqlsgsessergsqdfypkwreskl fit

KCN6q_     DEEVGPEETETDTFDAAPQPAREAAFASDSLRTGRSRSSQSICKAGESTDALSLPHVKLK
KCNQ4_     ............................................................
consensus  deevgpeetetdtfdaapqparesafasdslrtgrsrssqsickagestdalslphvklk
```

FIGURE 4B

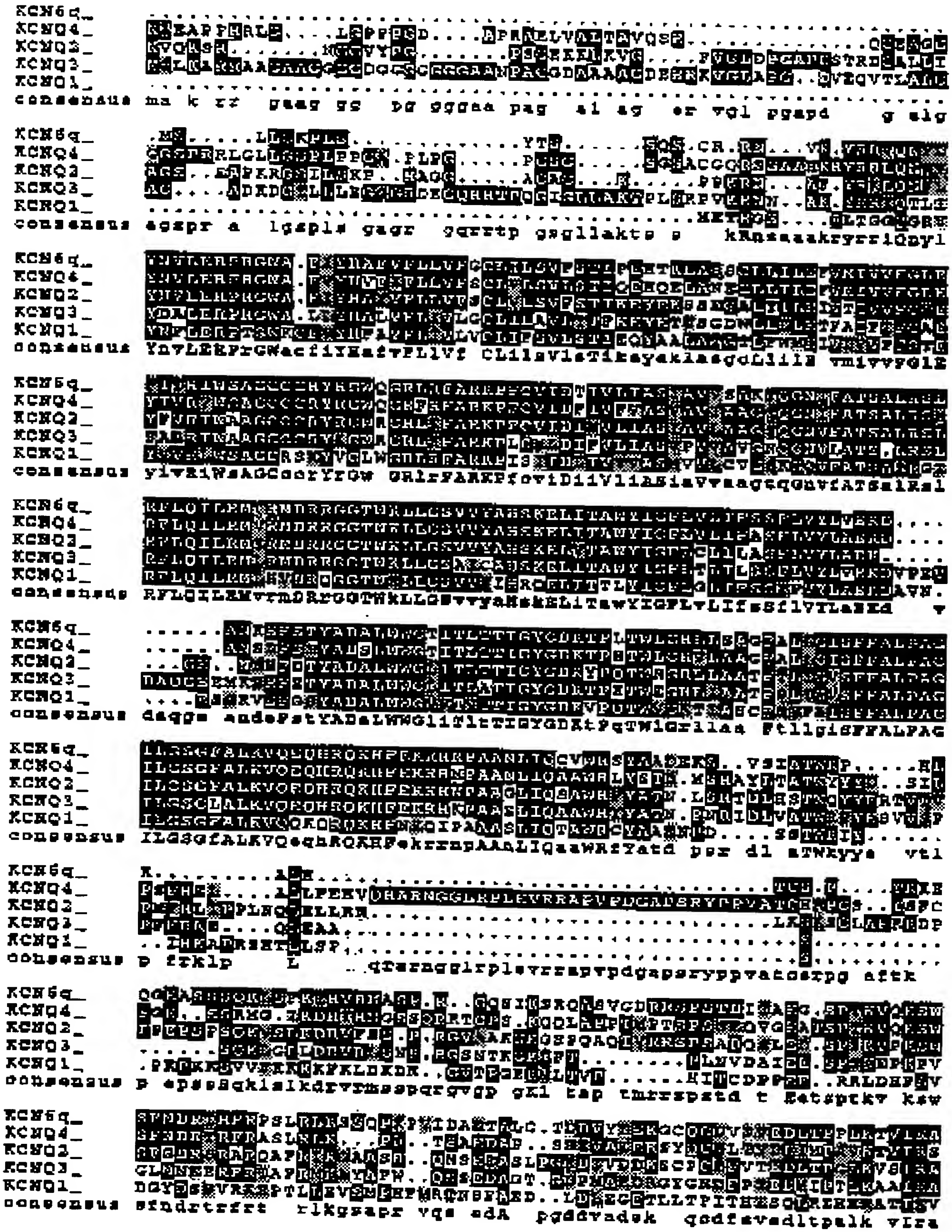


FIGURE 7C


KCN6q_
KCNQ4_
KCNQ2_
KCNQ3_
KCNQ1_
consensus irimkflvaKtKFketlrPYDVkDVIEqYSaGHLdmlsRIKsLQtRvDqivgkgp it
consensus kk rekg ftfpsqqeprn p esavp seiedlsmmgrvvkVEkqVqsiekkLd ll
consensus diymqvlrkg sas lt sypqigafepsq sdyhspvDsk yvdlsgsaq a tiers
consensus ts gsrglq ppe saqtfyalpp q t is e p n prng gts
consensus p ps gtlq pp ps lsrp tl sg esisdvttclrss s vqv q dl
consensus g s r s r tlrsvcpdvpsdt isl svqnlirshesiers sgfsisqsrs
consensus dfl ss fi d r yiaegetdtdsd tp g p satgeg sdslwtg k
consensus qsickagastdalslphvklk